Close relationship between mediators of inflammation and pancreatic cancer: Our experience

Vescio F et al. Relationship between inflammation and pancreatic cancer

Abstract
In this editorial we focus specifically on the mechanisms of the pancreatic inflammation affects pancreatic cancer. Cancer of the pancreas remains one of the deadliest cancer types. The highest incidence and mortality rates of pancreatic cancer are found in developed countries. Trends for pancreatic cancer incidence and mortality varied considerably in the world. A better understanding of the etiology and identifying the risk factors is essential for the primary prevention of this disease. Pancreatic tumors are characterized by a complex microenvironment that orchestrates metabolic alterations and supports a milieu of interactions among various cell types within this niche. In this editorial, we highlight the foundational studies that have driven our understanding of these processes. In our experimental centre, we have carefully studied the mechanisms between pancreatic inflammation and pancreatic cancer. We focused on the role of mast cells (MCs). MCs contain proangiogenic factors, in particular tryptase, which are associated with increased angiogenesis in various tumours. In this editorial we address the role of MCs in angiogenesis in both pancreatic ductal adenocarcinoma tissue and adjacent normal tissue. By assessing, the density of c-Kit receptor positive MCs, the density of tryptase positive MCs, the area of tryptase positive MCs, and angiogenesis in terms of microvascularisation density.

Key Words: Mast cells; C-Kit receptor; Tryptase; Angiogenesis; Microvascular density; Endothelial area; Pancreatic tumour tissue; Adjacent normal tissue

**Core Tip:** In this editorial we focus on the mechanisms linking pancreatic inflammation to pancreatic cancer. Pancreatic cancer remains one of the most aggressive pathologies. A better understanding of its etiology and identification of risk factors are essential for primary prevention. Mast cells (MCs) contain proangiogenic factors, particularly tryptase, which are associated with increased angiogenesis. We evaluated the role of MCs in angiogenesis in both pancreatic ductal adenocarcinoma tissue and adjacent normal tissue by assessing the density of c-Kit receptor-positive MCs, the density of tryptase-positive MCs, the area of tryptase-positive MCs, and angiogenesis in terms of microvascularisation density.

**INTRODUCTION**

The pancreas is an organ belonging to the digestive system located in the retroperitoneum, its location makes difficult the access both in instrumental diagnostics and in the surgical approach. The secretory function of acinar cells is carried out through the release of digestive enzymes: Amylase which digests carbohydrates, lipase which breaks down fats, trypsin and chymotrypsin which digest proteins. The endocrine component is made up of islet cells that release insulin and glucagon to maintain glycemic balance\(^1\).

The pancreas has a good reserve capacity, and the loss of its functionality is recognized only when the majority of the gland has been destroyed. The exocrine portion of the gland can suffer from three main diseases: Acute pancreatitis (AP), chronic pancreatitis (CP), and pancreatic ductal adenocarcinoma (PDAC)\(^2\).

In this editorial we will review the mechanisms linking CP and pancreatic cancer, outlining the possible causes involved in the transformation from benign to malignant pancreatic disease to achieve an early diagnosis.

PDAC, indeed, is characterized by poor prognosis due to late diagnosis, early metastases, and resistance to therapy. Although there have been improvements in
both diagnosis and treatment in recent years, the outcomes remain poor, with a 5-year overall survival of only 10.8%\cite{5}. Surgery remains the only potential for cure for resectable PDAC.

Pancreatitis is a fibro-inflammatory disorder of the pancreas due to the activation of digestive enzymes in the pancreas prior to their release into the small intestine resulting in parenchymal injury, inflammation, and abdominal pain. AP or CP may be related to autoimmunity or hyperlipidemia. A controlled diet and reduction of alcoholic beverages and cigarette smoking are useful in limiting the progression of pancreatitis from acute to chronic\cite{6}.

Repeated episodes of AP lead to CP, in which irregular secretion and premature activation of enzymes result in increased damage to the residual pancreas resulting in severe maldigestion and diabetes.

Histopathological features of CP include chronic inflammation, acinar atrophy, adipose tissue replacement, fibrosis, and abnormal ducts\cite{5,6}.

Pancreatitis has been shown to be a risk factor for pancreatic cancer\cite{5,6-9}.

In the pathophysiology of acute and CP leading to necrosis and fibrosis of acinar cells an important factor is represented by oxidative stress and the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS).

ROS and RNS, causing DNA fragmentation, membrane disintegration and protein misfolding, activate the immune system; immune cells and other stromal components produce inflammatory cytokines and chemokines which, together with ROS and RNS, cause epithelial cell damage and increased proliferation\cite{10}. Cytokines operate also in cell signaling and are the primary operators in defining the inflammation state of the tumor microenvironment\cite{11,12}. In a recent study Lanki et al\cite{13} analyzed 231 patients, 186 with stage I-III PDAC and 45 with CP through a serum panel including 48 inflammatory cytokines, carbohydrate antigen 19-9 (CA19-9), and C-reactive protein (CRP) with the aim of identifying the inflammatory cytokines present differently in the two pathologies. They concluded that the inflammatory cytokines CTACK, GRO-α, and β-NGF together with CA19-9 and CRP may help distinguish PDAC from CP. Other inflammatory mediators, such as cyclooxygenase-2, NF-jB, and STAT3, are involved in the inflammatory infiltration
and damage of acinar cells[14]. Numerous studies have highlighted how inflammatory stimuli in animals carrying an oncogenic Kras mutation activates a positive feedback mechanism that amplifies Ras activity to pathological levels, which determines the trigger of chronic inflammation and preneoplastic lesions[15]. Ling et al[16] demonstrated that the Kras oncogene induces the constitutive activation of signals necessary for the establishment of PDAC. Finally, another study demonstrated that in a Kras mutant context, TNF-α-induced activation of the NF-κB pathway maintains transformed cells in a constant inflammatory state[17]. The immune system has great potential in reducing tumors; however, its dysregulation could lead to tumor spread and reduced survival of individuals.

At our research center, we have studied the mechanisms between pancreatitis and pancreatic cancer in detail. We have focused on the role of mast cells (MC). MC are bone marrow-derived cells found in many human organs and tissues and contain many pre-existing and newly formed secretory granules with specific pleiotropic functions[18].

The function of MC is especially regulated by their membrane receptor tyrosine kinase, the c-Kit receptor (c-Kit-R), which naturally binds stem cell factor. MCs are activated by various stimuli[19] once activated, MCs release their secretory granules to the microenvironment. Recently, various research groups have shown that MCs contain several pro-angiogenic factors, including the ability to synthesize and secrete a potent pro-angiogenic factor called tryptase. Tryptase is the most abundant factor stored in the secretory granules of MCs can stimulate microvascular formation.

In our studies, through immunohistochemistry and image analysis system, we analyzed the concentration of MCs positive for the c-Kit-R, the concentration of MC positive for tryptase, the area of MC positive tryptase, microvascular density (MVD), and endothelial area in a series of pancreatic cancer patients undergoing radical surgery. The correlation between the parameters studied and the main clinical-pathological characteristics was also investigated[20-22].

**CONCLUSION**
Conclusions from these preliminary data collected would appear that MC granules contain an enormous quantity of protease enzymes which, through different mechanisms, they induce the formation of new microvessels, fueling the tumor load. Numerous studies suggest that MC density growth is associated with MVD microvascular density growth in several malignancies. Survival of patients with resected pancreatic cancer, demonstrating that high expression of MVD microvascular density is strongly associated with a worse prognosis. Preliminary in vivo/in vitro results have been obtained by other researchers. Their data suggest that therapeutic targeting of MC degranulation factors could be a novel strategy to inhibit tumor growth and neo-angiogenesis.

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