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

Francesca Vescio, Michele Ammendola, Giuseppe Currò, Silvia Curcio

Abstract

In this editorial, we focus specifically on the mechanisms by which 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 of pancreatic cancer incidence and mortality vary considerably worldwide. A better understanding of the etiology and identification of 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 center, we have carefully studied the mechanisms of that link pancreatic inflammation and pancreatic cancer. We focused on the role of mast cells (MCs). MCs contain pro-angiogenic factors, including tryptase, that are associated with increased angiogenesis in various tumors. In this editorial, we address the role of MCs in angiogenesis in both pancreatic ductal adenocarcinoma tissue and adjacent normal tissue. The assessment includes 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 microvascularization density.

Key Words: Mast cells; C-Kit receptor; Tryptase; Angiogenesis; Microvascular density; Endothelial area; Pancreatic tumor tissue; Adjacent normal tissue
Core Tip: This editorial focuses on the mechanisms that link pancreatic inflammation to pancreatic cancer. Pancreatic cancer remains one of the most aggressive pathologies. A better understanding of its etiology and the identification of risk factors is essential for primary prevention. Mast cells (MCs) contain pro-angiogenic factors, particularly tryptase, that 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 e-Kit receptor-positive MCs, the density of tryptase-positive MCs, the area of tryptase-positive MCs, and microvascularization density.

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INTRODUCTION

The pancreas is an organ belonging to the digestive system located in the retroperitoneum. Its location makes it difficult to access both in instrumental diagnostics and in the surgical approach. Pancreatic acinar cells secrete digestive enzymes including amylase, which digests carbohydrates; lipase, which breaks down fats; and 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, has a 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%. Surgery remains the only potential cure for resectable PDAC. Pancreatitis is a fibro-inflammatory disorder of the pancreas that involves 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[4]. 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 maligestion and diabetes.

Histopathological features of CP include chronic inflammation, acinar atrophy, adipose tissue replacement, fibrosis, and abnormal ducts[5,6]. Pancreatitis has been shown to be a risk factor for pancreatic cancer[7-9]. In the pathophysiology of AP and CP, oxidative stress and the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) lead to necrosis and fibrosis of acinar cells. ROS and RNS cause DNA fragmentation, membrane disintegration, and protein misfolding. They also 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[10]. Cytokines operate in cell signaling and are the primary operators in defining the inflammation state of the tumor microenvironment[11,12]. In a recent study, Lanki et al[13] analyzed 231 patients, 186 with stage I-III PDAC and 45 with CP with a serum panel including 48 inflammatory cytokines, carbohydrate antigen 19-9 (CA19-9), and C-reactive protein (CRP) to identify differences the inflammatory cytokines present 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-κB, and STAT3, were involved in inflammatory infiltration and damage of acinar cells[14]. Numerous studies have highlighted how inflammatory stimuli in animals carrying an oncogenic Kras mutation activate a positive feedback mechanism that amplifies Ras activity to pathological levels and triggers 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 the presence of a Kras mutant, TNF-α-induced activation of the NF-κB pathway maintained transformed cells in a constant inflammatory state[17]. The immune system has great potential for reducing tumors, but its dysregulation can lead to tumor spread and reduced survival of individuals.

THE PRESENCE OF MAST CELLS IS COMMON IN THE INFLAMMATORY ENVIRONMENT OF PANCREATITIS AS WELL AS PANCREATIC CANCER

At our research center, we have studied the mechanisms that link pancreatitis and pancreatic cancer in detail. We have focused on the role of mast cells (MCs), which 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. After activation by various stimuli[19], MCs release their secretory granules into the microenvironment. Recently, various research groups have shown that MCs contain several pro-angiogenic factors and synthesize and secrete a potent pro-angiogenic factor called tryptase. Tryptase is the most abundant factor stored in the secretory granules of MCs it can stimulate microvessel formation. Our studies have used immunohistochimistry and image analysis to determine the concentration of MCs positive for c-Kit-R, the number of MCs 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 and pathological characteristics was also investigated[20-22].

CONCLUSION

Conclusions from these preliminary data suggest that MC granules contain many protease enzymes that, by different mechanisms, induce the formation of new microvessels that supply the tumor load. Numerous studies suggest that MC density growth is associated with MVD growth in several malignancies. A study of survival of patients with resected pancreatic cancer demonstrated that high expression of MVD was closely associated with a worse prognosis[23]. 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.

FOOTNOTES

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