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Pancreatic Cancer and Inflammation

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Abstract

The association between cancer and inflammation is arguably undeniable. However, it is uncertain whether inflammation leads to cancer development or oncogenic changes result in inflammatory conditions. Regardless of the debate surrounding this argument, inflammation in the immediate vicinity of the tumor promotes its development and makes inflammatory markers attractive targets both for prevention as well as treatment. This review discusses the role of inflammation in pancreatic cancer, one of the most lethal cancers with the lowest survival rates. Risk factors associated with pancreatic cancer have an underlying inflammatory pathology. The mechanisms that influence cellular damage including signaling pathways in pancreatitis and pancreatic cancer will be briefly discussed.

Keywords: Inflammation; Pancreatic Cancer; Pancreatitis, Smoking; Alcohol; Obesity.

Introduction

Although the concept is more than a century old, in recent years there has been a renewed interest in linking inflammation and cancer based on epidemiological studies in humans and evidence from genetically engineered mouse models [1, 2]. Chronic inflammation, triggered by infections, autoimmune disorders and other etiological factors of unknown origin, has been proposed as a contributory factor in the development of various cancers [1]. Evidence for this association is reinforced through studies that have demonstrated decrease in the incidence of and mortality from several cancers by the use of non-steroidal anti-inflammatory drugs. Signs of inflammation within the tumors include inflammatory cells and inflammatory mediators and understanding the signaling pathways triggered by these events would allow the development of therapeutic strategies that

simultaneously target the tumor as well as the tumor microenvironment.

Pancreatic cancer

Pancreatic cancer is the most lethal of all cancers [3]. An estimated 42,470 new cases of pancreatic cancer are predicted to occur in the United States with an estimated 35,240 deaths expected in the year 2009 [3]. Although incidence and death rates of pancreatic cancer have been stable in men since 1993, they have been increasing in women by 0.6% and 0.1% per year respectively [3]. Pancreatic cancer develops without early symptoms and is most often diagnosed at very advanced stages. Tobacco smoking increases the risk with incidence rates being more than twice as high for cigarette smokers than for nonsmokers. Risk also appears to increase with obesity, chronic pancreatitis, diabetes, cirrhosis, and possibly with the use of smokeless tobacco. A family history of pancreatic cancer also increases risk [3]. Though evidence is still accumulating, consumption of red meat is associated with increased risk and physical activity may decrease the risk. For all stages combined, the 1- and 5-year relative survival rates are 24% and 5%, respectively. Even for patients diagnosed with local disease, the 5-year survival is only 20% [3]

Pancreatic cancer and inflammation

The etiology of pancreatic cancer is not completely known, however there is compelling evidence suggesting the role of inflammation in pancreatic carcinogenesis [4]. Inflammation is a natural response of the body to injury and is essential for wound healing. It activates the immune system to neutralize infectious agents through mobilization of effector cells and release of several chemotactic cytokines. A downside to this response is the development of neoplasia especially if the inflammatory response becomes chronic. A chronic inflammatory state favors gene alterations and subsequently leads to initiation of carcinogenesis [4, 5]. Several inflammatory mediators that contribute to cancer development have been identified. Reactive oxygen species and other free radicals may contribute to cancer initiation through oxidative damage and nitration of DNA thus inducing mutations [6]. In areas with tissue damage, inflammatory responses could send survival and proliferative signals to cells repopulating the damaged area, leading to the promotion of the growth of healthy tissues as well as tumors [4-7].

Pancreatic tumors over-express cyclooxygenase-2 (COX-2), a universal modulatory molecule in inflammation, which has also been implicated in the process of tumorigenesis [8]. Studies have demonstrated a protective role of non-steroidal anti-inflammatory medications against many cancer types [9].

Pancreatitis

Inflammation within the pancreas is commonly referred to as pancreatitis. Chronic pancreatitis is induced by several factors resulting in tissue destruction and gradual replacement of the pancreatic gland with fibrotic tissue [4, 10]. Several factors such as genetic, excessive alcohol consumption and cigarette smoking predispose individuals to develop pancreatitis [11-13]. Hereditary pancreatitis is a rare condition that affects young children [14]. It is caused in the majority of cases by mutations in the cationic trypsinogen gene (*PRSSI*). As a consequence of this mutation, premature activation or impaired deactivation of trypsin occurs thereby resulting in recurrent injury and inflammation in the pancreas. Several mutations within the *PRSS1* gene have been identified with 70% of mutations attributed to R122H and N29I [13, 15, 16]. In R122H mutation, the arginine to histidine amino acid substitution at the 122 residue, results in a gain-of-function activity preventing trypsin's inactivation. In a subset of hereditary pancreatitis patients the lifetime risk of developing pancreatic cancer could be as high as 40% with the risk being strongly associated with the duration of chronic inflammation [17].

Hereditary pancreatitis patients who are also smokers are prone to pancreatic cancer and develop pancreatic cancer an average of 20 years earlier than non-smokers [17]. In a recent study, PRSS1 mutations were detected in 68% of

hereditary pancreatitis patients [16]. In this study, at ages 50 and 75 years, the cumulative risk of being diagnosed with pancreatic adenocarcinoma in patients with chronic hereditary pancreatitis was 11% and 49% for men and 8% and 55% for women, respectively.

Pancreatic cancer often involves somatic activation of K-Ras oncogenes (18). It has been reported that selective expression of an endogenous K-Ras oncogene in embryonic cells of acinar/centroacinar lineage results in pancreatic intraepithelial neoplasia and invasive adenocarcinoma. Surprisingly, adult mice become refractory to K-Ras-induced pancreatic neoplasia and cancer. However, if mice are challenged with a mild form of chronic pancreatitis, they develop the full spectrum of pancreatic intraepithelial neoplasia and invasive adenocarcinoma. These observations imply that, during adulthood, pancreatic adenocarcinoma stems from a combination of genetic and non-genetic events (19).

Pancreatitis as a consequence of alcohol consumption leads to destruction of the pancreatic parenchymal tissue [20]. Individuals who drink five or more glasses of alcohol are at a heightened risk for the development of chronic pancreatitis [12]. Alcohol abuse lowers the threshold for acute pancreatitis, [13] and cigarette smoking potentiates the chronic inflammatory process [4, 13]. Acinar cells in the pancreas respond to tissue injury by releasing pro-inflammatory mediating molecules [21] that also results in activation of activator protein-1 (AP-1), nuclear factor-κB (NF-κB), p38 MAP kinase and other transcription factors [22, 23]. Rats prone to the development of experimental pancreatitis [22] and given alcohol exhibit greater amounts of pancreatic necrosis and observed to have increased levels of pro-inflammatory cytokines, and greater activation of AP-1, NF-κB and trypsin. It is suggested that macrophages play an important role in the alcohol-mediated fibrosis [23, 24]. In particular macrophages (CD68+) are closely associated with activated pancreatic stellate cells which are responsible for the fibrosis [25].

Alcohol consumption in itself predisposes pancreas to inflammation through release of toxic metabolic byproducts. Alcohol metabolism through non-oxidative pathway involves esterification of ethanol with fatty acids to form fatty acid ethyl esters which accumulate in the pancreas and promote the release of endogenous hydrolases from pancreatic lysosomes which are capable of converting trypsinogen to trypsin, thus predisposing to intrapancreatic autodigestion and pancreatitis [21]. Alcohol metabolism by the oxidative enzyme system (alcohol dehydrogenase or the cytochrome P450 system) generates reactive oxygen species resulting in tissue injury, NF-κB activation and release of proinflammatory cytokines [22]. Excessive alcohol consumption can also lead to cell death within the pancreas. This cell death, necrotic in nature can cause acute and chronic pancreatitis through release of pro-inflammatory metabolites contributing to tissue injury predisposing the tissue to cancer initiation.

The greatest risk for pancreatic cancer development is perhaps cigarette smoking. Individuals who smoke cigarettes are at a risk for the development of both chronic pancreatitis as well as pancreatic cancer. Cigarette smoke is supposed to be a dump yard for carcinogenic chemicals some of which include N-nitrosamines, nicotine, tar, arsenic etc [26]. These carcinogens can induce DNA mutations; formation of damaging DNA adducts and ultimately leads to an inflammatory reaction [26].

Nicotine may also play a role in intra-pancreatic inflammation by increasing pancreatic protein synthesis in isolated acini, inducing cytoplasmic vacuolation and cellular edema in the exocrine pancreatic regions [27, 28]. Cigarette smokers have elevated levels of systemic markers of inflammation, including myeloperoxidase, lipocalin and C-reactive protein [29, 30]. These metabolic changes may explain the increased incidence of pancreatic cancer in cigarette smokers.

There is convincing evidence that insulin resistance or post load serum glucose concentration may cause pancreatic cancer [31, 32]. In a landmark study, 1.3 million people were followed for a period of 10 years and it was observed that individuals with the greatest fasting glucose levels (>140 mg/dL) had the greatest fatality rates from cancer after adjusting for tobacco smoking and alcohol consumption.

Interestingly, the risk associations with fasting glucose levels were greatest for pancreatic cancer [31]. It is suggested that insulin and insulin-like growth factors may be responsible for the increased risk of cancer noted in obese patients [33]. Studies have also observed an increase in the expression of insulin receptors in many types of cancer, including pancreatic cancer [34]. There is evidence that diabetes causes neoplasia. In a study with metformin, a drug prescribed to improve insulin resistance, there was no evidence of pancreatic neoplasia compared to the control group where malignant pancreatic tumors developed [35]. A 16 year, prospective study that included over 1 million individuals who were free of cancer at baseline indicated diabetes as an independent predictor of mortality from cancer of the colon, pancreas, female breast, and, in men, of the liver and bladder [36]. Type II diabetes can lead to pancreatic cancer and it has been observed that four out of five individuals have glucose intolerance or obvious diabetes at the time of their pancreatic cancer diagnosis [37, 38]. In a prospective randomized clinical trial, middle-aged women free of type II diabetes, heart disease or cancer were enrolled. After four years, study investigators noted that elevated levels of C-reactive protein and IL-6 predicted the development of type II diabetes, supporting a possible role for inflammation in diabetogenesis [39].

Obesity and pancreatic cancer have been observed to be related. A large prospective study in the United States men and women noted a 45% increased risk of pancreatic cancer for participants having a body mass index of ≥35 compared to those with a body mass index of 18.5-<25. Two recent prospective studies documented that significantly increased waist to hip ratio was associated with an elevated risk of pancreatic cancer [40, 41]. It is suggested that the elevated cancer risks in obese individuals may be a product of the low-grade systemic inflammation that occurs subsequently to adipose tissue-specific synthesis of inflammatory soluble molecules [42]. Obese individuals have higher circulating levels of the pro-inflammatory adipokines resistin and leptin and lower circulating levels of the anti-inflammatory adipokine, adiponectin [42].

Conclusions

Inflammation with a slow onset and that persists for long durations is termed as chronic. Chronic inflammation may occur by itself or follow on from an acute inflammatory bout. While inflammation is natural response of the body to neutralize infections and foreign objects long term persistence could lead to tissue damage interrupting normal cellular homeostasis and may promote the initiation of neoplasia. A variety of conditions associated with systemic and intrapancreatic inflammation have been shown to contribute to the risk of developing pancreatic cancer. Chronic pancreatitis is associated with increased pancreatic cancer risk while alcohol consumption, obesity and cigarette smoking likely require additional stimuli to induce pancreatic carcinogenesis. Behavioral modifications including not smoking cigarettes, drinking alcohol only in moderation and maintaining a healthy weight could help to decrease the likelihood of developing this rare but highly fatal form of cancer. The use of metformin as a cancer protective drug suggests that research initiatives should include the use of targeted anti-inflammatory therapies in the prevention and treatment, especially among individuals who are at increased risk for the development of pancreatic cancer.

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