Obesity, Intrapancreatic Fatty Infiltration, and Pancreatic Cancer

Hua Wang¹, Anirban Maitra²,³,⁴ and Huamin Wang²,³

¹Department of Gastrointestinal Medical Oncology, ²Department of Pathology, ³Department of Translational Molecular Pathology, ⁴Sheikh Ahmed Bin Zayed Al Nahyan Center for Pancreatic Cancer Research, University of Texas M.D. Anderson Cancer Center, Houston Texas

Corresponding Author: Huamin Wang, Department of Pathology and Department of Translational Molecular Pathology, Unit 085, The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030. Phone: 713-563-1846; Fax: 713-563-1848; E-mail: hmwang@mdanderson.org

Running title: Obesity and Pancreatic Cancer

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.
Summary

Obesity and intrapancreatic fatty infiltration are associated with increased risk of pancreatic cancer and its precursor lesions. The interplay amongst obesity, inflammation, and oncogenic Kras signaling promotes pancreatic tumorigenesis. Targeting the interaction between obesity-associated inflammation and Kras signaling may provide new strategies for prevention and therapy of pancreatic cancer.
In this issue of *Clinical Cancer Research*, Rebours and colleagues (1) report that fatty infiltration in normal pancreas is associated with the body mass index (BMI), and the percentages of total fat area (TFA), visceral fat area (VFA), and subcutaneous fat area (SFA) in 110 patients who underwent pancreatic resection for well-differentiated pancreatic neuroendocrine tumors. They demonstrate that intralobular fibrosis and intralobular fatty infiltration of the pancreas is independently associated the presence of pancreatic intraepithelial neoplasia (PanIN), the precursor lesions of pancreatic ductal adenocarcinoma. The number of PanIN lesions increases with the severity of hepatic steatosis and the percentage of intrapancreatic fatty infiltration, but not with the percentage of SFA or BMI (1). This study provides a direct link between obesity, intrapancreatic fatty infiltration and the risk of pancreatic cancer precursor lesions. Consistent with the findings from this study, prior reports have similarly underscored the deleterious association between intrapancreatic fatty infiltration with the increased risk of pancreatic ductal carcinoma (2). The association between obesity and the increased risk of pancreatic cancer has been well documented by both epidemiologic and experimental studies. In a large case-control study by Silverman et al., obesity was associated with 50%-60% increased risk of pancreatic cancer in both man and women. Compared to the group with lowest quartile of BMI and caloric intake, the group with highest quartile of BMI and caloric intake had a 180% higher risk of pancreatic cancer (3). In a pooled analysis of 2170 cases and 2209 control subjects from the Pancreatic Cancer Cohort Consortium (PanScan), the adjusted odd ratio (OR) for pancreatic cancer for the highest vs lowest quartile of BMI was 1.33 (95% CI, 1.04-1.69) and 1.34 (95% CI, 1.05-1.70) in men and women respectively (4). Overweight or obesity during early adulthood was associated not only with an increased risk of pancreatic cancer, but also the early onset of disease. In patients with pancreatic cancer, obesity was associated with poor survival (5). High
fat diet (HFD) has been shown to promote the growth and tumor cell turnover of human pancreatic cancer cells in an orthotopic xenograft study (6). These studies provided strong evidence that the obesity, particularly android obesity, and intrapancreatic fatty infiltration are associated with increased risk of pancreatic cancer and play an important role in pancreatic tumorigenesis.

The underlying mechanisms how obesity drives pancreatic tumorigenesis are unclear. Adipose tissue actively secretes various adipokines, cytokines, and chemokines. It has been postulated that obesity and excess visceral fat infiltration induce a chronic inflammation state through these adipokines and cytokines and promote the development of pancreatic cancer. Consistent with this notion, Hori et al. showed that Syrian golden hamsters fed with HFD had hyperlipidemia and increased intrapancreatic fatty infiltration. At 7 weeks after N-nitrosobis(2-oxopropyl)amine (BOP) treatment, pancreatic dysplasia and adenocarcinoma developed in 78% and 67%, respectively, in the hamsters fed with HFD compared to 25% and 0%, respectively, in those fed with standard diet. HFD increases the expression levels of adipocytokines, inflammatory factors and growth-related genes, such as monocyte chemoattractant protein 1, IL-1β, COX-2, insulin, insulin like growth factor 1 (IGF-1), and cyclin D1 in the pancreas in the BOP + HFD group (7). Using a genetically engineered mouse model, Philip et al. showed that the LSL-Kras/Ela-CreERT mice fed with HFD for 30 days had increased Kras activity, increased expression of cyclooxygenase-2 (COX-2) and downstream activation of Erk. These mice developed greater severity of chronic pancreatitis and harbored six-fold higher PanIN lesions than those fed with control diets. Long-term consumption of HFD accelerated the progression from low-grade PanINs to high-grade PanINs and invasive pancreatic ductal adenocarcinoma, and decreased the survival rate and survival time of LSL-Kras/Ela-CreERT mice compared to
those fed with control diet. Treatment with a COX-2 inhibitor, celecoxib, or conditional knockout of COX-2 in LSL-Kras/Ela-CreERT mice effectively prevented the above-mentioned effects of HFD on pancreatic tumorigenesis. These findings suggest that, on the one hand oncogenic Kras elevates pro-inflammatory factors like COX-2, while on the other hand, HFD further enhances the activity of oncogenic Kras via COX-2, thereby setting into motion a feed forward loop that results in increased severity of murine PanINs and pancreatic cancer (8). On the other hand, calorie restriction prevents obesity and inhibits the growth of both mouse Panc02 allografts, as well as human pancreatic cancer xenografts. Mice on calorie restriction had decreased serum IGF-1 levels, decreased expression of the pro-inflammatory genes, such as S100a9, F4/80, and macrophage chemoattractant, Ccl2. The inhibitory effects of calorie restriction on pancreatic cancer growth were postulated to be due to reduced NFκB activation mediated through the IGF-1 signaling pathway (9). Therefore, the interplay amongst the HFD/obesity axis and altered metabolic activities, inflammation, and oncogenic Kras signaling promote the development of chronic pancreatitis, PanIN lesions and progression to invasive pancreatic cancer (Fig. 1).

Progressive intrapancreatic fatty infiltration is one of the main histopathologic changes in patients with hereditary pancreatitis secondary to germline PRSS1 mutations, an autosomal dominant disorder that is associated with very high-risk of pancreatic cancer (10). In these patients, the intrapancreatic fatty infiltration seems be secondary to the extensive loss of pancreatic acinar cells due to repeated episodes of acute and chronic pancreatitis. However, the mechanism of intrapancreatic fatty infiltration in obese patients remains to be determined. Recent study by Grippo et al showed that knockout of pigment epithelium-derived factor (PEDF) in EL-KrasG12D mice resulted in increased intrapancreatic fatty infiltration and peripancreatic fat
with adipocyte hypertrophy. The expression levels of lipid droplet associated proteins, tail-interacting protein 47 (TIP47) and adipose differentiation-related protein (ADRP) were increased, while the expression of adipose triglyceride lipase, a key enzyme in lipolysis, was decreased in pancreatic stroma of EL-KrasG12D/PEDF deficient mice. Compared to the EL-KrasG12D/PEDF wild type mice, EL-KrasG12D/PEDF null mice had higher frequencies of cystic papillary neoplasms and invasive pancreatic ductal adenocarcinoma (11). Their study shed the light on the mechanism of intrapancreatic fatty infiltration. The relationship between the intrapancreatic fatty infiltration and the development of cystic papillary neoplasms and pancreatic ductal adenocarcinoma was not clear in their study.

Obesity and diabetes are two major modifiable risk factors for pancreatic cancer. The antidiabetic drug metformin has been shown to have antitumor activity for pancreatic cancer (12). Blockage of the positive feedback loop between the obesity-associated inflammation and oncogenic Kras may provide new strategies for the prevention or therapy of pancreatic cancer. Weight reduction, reducing the consumption of HFD, administration of COX-2 inhibitors may reduce the inflammation and fibrosis of the pancreas and prevent the initiation of PanIN lesions and their progression to pancreatic cancer.

References


Figure 1. The interplay amongst high fat diet/obesity, inflammation, and oncogenic Kras signaling promotes pancreatic tumorigenesis
Figure 1:

High-fat diet
Obesity

Inflammation

Adipokines
Cytokines
Pro-Inflammatory factors

Inflammatory mediators

IGF-1

Activation of oncogenic Kras signaling

NFκB
ERK
COX-2

Chronic pancreatitis
Proliferation
PanIN lesions

Pancreatic cancer

© 2015 American Association for Cancer Research

CCR Translations
AAGC

© 2015 American Association for Cancer Research

Intrapancreatic fatty infiltration

COX-2 inhibitor
Obesity, Intrapancreatic Fatty Infiltration, and Pancreatic Cancer

Hua Wang, Anirban Maitra and Huamin Wang

*Clin Cancer Res*  Published OnlineFirst May 20, 2015.

Updated version
Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-15-0718

Author Manuscript
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.