

# Obesity, Intrapancreatic Fatty Infiltration, and Pancreatic Cancer

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Obesity and intrapancreatic fatty infiltration are associated with increased risk of pancreatic cancer and its precursor lesions. The interplay among obesity, inflammation, and oncogenic Kras signaling promotes pancreatic tumorigenesis. Targeting the inter-

action between obesity-associated inflammation and Kras signaling may provide new strategies for prevention and therapy of pancreatic cancer. *Clin Cancer Res*; 21(15); 3369–71. ©2015 AACR.

See related article by Rebours et al., p. 3522

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, visceral fat area, 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 are independently associated with 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 and colleagues (3), obesity was associated with 50% to 60% increased risk of pancreatic cancer in both men and women. Compared with the group with the lowest quartile of BMI and caloric intake, the group with the highest quartile of BMI and caloric intake had a 180% higher risk of pancreatic cancer (3). In a pooled analysis of 2,170 cases and 2,209 control subjects from the Pancreatic Cancer Cohort Consortium (PanScan), the adjusted odds ratio (OR) for pancreatic cancer for the highest versus lowest quartile of BMI was 1.33

[95% confidence interval (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 with 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 and colleagues (7) 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 with 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, IL1 $\beta$ , 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 and colleagues (8) showed that the LSL-Kras/Ela-CreERT mice fed with HFD for 30 days had increased Kras activity, increased expression of COX-2 and downstream activation of Erk. These mice developed greater severity of chronic pancreatitis and harbored 6-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 with 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

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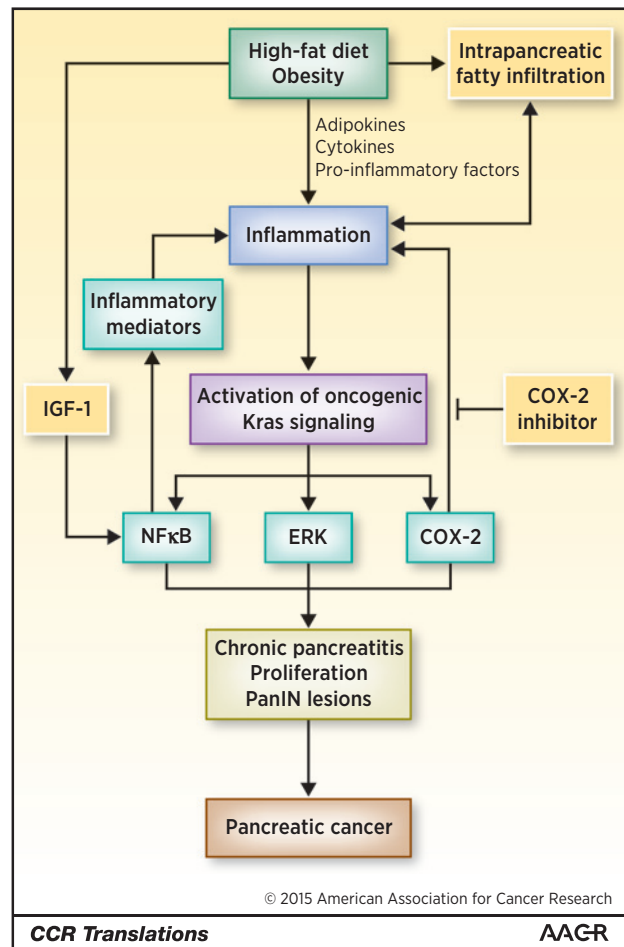
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findings suggest that, on the one hand, oncogenic Kras elevates proinflammatory factors such as COX-2, while, on the other hand, HFD further enhances the activity of oncogenic Kras via COX-2, thereby setting into motion a feed-forward loop that results 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 and human pancreatic cancer xenografts. Mice on calorie restriction had decreased serum IGF-1 levels, decreased expression of the proinflammatory 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 NF $\kappa$ B activation mediated through the IGF-1 signaling pathway (9). Therefore, the interplay among the HFD/obesity axis and altered metabolic activities, inflammation, and oncogenic Kras signaling promotes 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 to 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. A recent study by Grippo and colleagues (11) showed that knockout of pigment epithelium-derived factor (PEDF) in EL-Kras<sup>G12D</sup> 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 the pancreatic stroma of EL-Kras<sup>G12D</sup>/PEDF-deficient mice. Compared with the EL-Kras<sup>G12D</sup>/PEDF wild-type mice, EL-Kras<sup>G12D</sup>/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, and administration of COX-2 inhibitors may reduce the inflammation and



**Figure 1.** The interplay among HFD/obesity, inflammation, and oncogenic Kras signaling promotes pancreatic tumorigenesis.

fibrosis of the pancreas and prevent the initiation of PanIN lesions and their progression to pancreatic cancer.

#### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

#### Authors' Contributions

Conception and design: A. Maitra  
 Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Huamin Wang  
 Writing, review, and/or revision of the manuscript: Hua Wang, A. Maitra, Huamin Wang

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