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Obesity-Related Effects on Pancreatic Disease

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Obesity is pervasive in western society, and its systemic effects extend to pancreatic disease. This chapter reviews the effects of obesity on pancreatic disease – specifically acute pancreatitis and pancreatic adenocarcinoma. Special focus is directed toward the influence of adipokines, biologically active proteins produced by adipose tissue.

1. Obesity and Adipose Tissue as a Metabolic Organ

Obesity has become a global epidemic in the 21st century. In America alone, over one-third of adults are currently obese, the incidence of obesity continues to rise, and obesity is occurring at younger ages (30,92). Obesity significantly increases the risk for numerous chronic diseases including insulin resistance, diabetes, cardiovascular disease, stroke, hyperlipidemia, arthritis, asthma, non-alcoholic steatohepatitis (NASH), and some forms of cancer (100). Adipose tissue expansion and infiltration into body tissues is accompanied by an altered leukocyte profile and subsequent induction of the local proinflammatory cytokine milieu. This milieu in turn generates a systemic proinflammatory state, the end results of which have been well documented in the pathogenesis of disease processes such as atherosclerosis (63) and NASH (39). It is intuitive that a similar process would affect the pancreas in obesity.

Early autopsy and radiology studies correlated obesity with increased pancreatic fat deposition (96,131). Fatty replacement of the pancreas in cystic fibrosis leads to severe exocrine insufficiency (51). In addition, in vitro studies have suggested that lipotoxicity in pancreatic β cells contributes to type II diabetes, though in vivo studies have been less convincing (128, 144). Moreover, clinical studies have shown obesity to be a risk factor for increased severity of acute pancreatitis (AP) and for developing pancreatic ductal adenocarcinoma (PDAC).

The increased incidence of obesity has led to a surge in basic obesity research. As a result, a greater understanding of the specific mechanisms by which obesity impacts clinical disease has begun to emerge. For many years, adipose tissue was viewed primarily as an inert storage depot where excess energy was packaged in the form of triglycerides, and released when needed in the peripheral tissues. The discovery of leptin in 1994 (143) and adiponectin shortly thereafter (109) marked the beginning of a dramatic change in this established concept. Leptin and adiponectin are proteins produced predominantly by adipocytes that have a broad ranging impact on diverse metabolic and inflammatory processes, and were thus termed adipokines. Over the subsequent decades, a number of other adipokines have been identified, and the paradigm of adipose tissue as an active metabolic organ has become widely accepted.

Adipokines

Adipose tissue is now recognized not simply as an energy storage depot, but as an active metabolic organ (44). Prominent among the 100 individual proteins produced by adipocytes are adipokines: small, cytokine-like molecules that modulate metabolism, inflammation, angiogenesis, and the immune response (68,122). The obese state is characterized by alteration in adipokine concentration and function. Adipokines' position upstream from several mechanisms that influence cancer growth, invasion, and metastasis make the perturbed adipokine milieu of obesity a logical link between obesity and accelerated cancer growth. Similarly, this position makes adipokines an attractive target for intervention – not simply at the level of the cancer cell, but upstream of several overlapping mitogenic pathways. Not surprisingly, a moderate amount of investigation has evaluated adipokines' role in tumor biology (5,37,48,113). The best studied adipokines to date are leptin and adiponectin.

Adiponectin is expressed in full length, multimeric, and globular forms; the precise role of these isoforms remains to be defined. Circulating adiponectin levels are in the microgram per milliliter range, which is about 2-5 orders of magnitude greater than observed with other adipokines and cytokines. This fact, along with its long half-life (about 14 hours), have positive implications for potential use as a therapeutic agent (101). Circulating adiponectin concentration paradoxically decreases with increasing obesity, a feedback loop that appears to be regulated by tumor necrosis factor alpha (TNF-α) (2,13,107). Two receptors for adiponectin, AdipoR1 and AdipoR2 were discovered in 2003 (139). AdipoR1 has been shown in several models to be expressed strongly in skeletal muscle and widely throughout various organ systems, while AdipoR2 appears to be predominantly expressed in liver. Both AdipoR1 and AdipoR2 have been identified in human and rodent pancreatic β cells, as well as throughout the embryonic murine gut (62,115,145). Our research group has recently documented the presence of AdipoR1 and AdipoR2 in murine pancreas. Adiponectin also modulates metabolism. Increased adiponectin enhances insulin sensitivity and increases fatty acid oxidation, effects that appear to be mediated through adenosine monophosphate kinase (AMPK) (33,123). In humans, decreased adiponectin levels lead to insulin resistance and development of cardiovascular disease (47,67).

In addition to its metabolic effects, emerging evidence has shown that adiponectin plays an important role in regulating the immune and inflammatory response **(Figure 1).** The initial anti-inflammatory effects of adiponectin were described in endothelial cells. In this system, adiponectin potently downregulates the expression of adhesion molecules intracellular adhesion molecule-1 (ICAM-1) and vascular cellular adhesion molecule-1 (VCAM-1) by inhibiting TNF-α (98,59). Adiponectin markedly reduces macrophage phagocytic activity andTNF-α production by inhibiting nuclear transcription factor κB (NF-κB) activation (80). Adiponectin also induces production of the important anti-inflammatory cytokines IL-10 and IL-1ra by human monocytes and macrophages, and repressed production of interferon-γ (IFN-γ) by LPS-stimulated human macrophages (97,137). Inhibition of NF- κB appears to be at least partly responsible for these effects, as well.

In vivo, adiponectin has been shown to have anti-inflammatory effects in various models of liver inflammation (80) and acute intestinal inflammation (28,87). These protective effects are mediated by downregulation of TNF-α and chemokine production, as well as by induction of anti-inflammatory IL-10. In obese humans, circulating adiponectin concentration correlates negatively with the inflammatory marker c-reactive protein and with levels of the pro-inflammatory cytokines TNF-α and IL-6 (13,107).

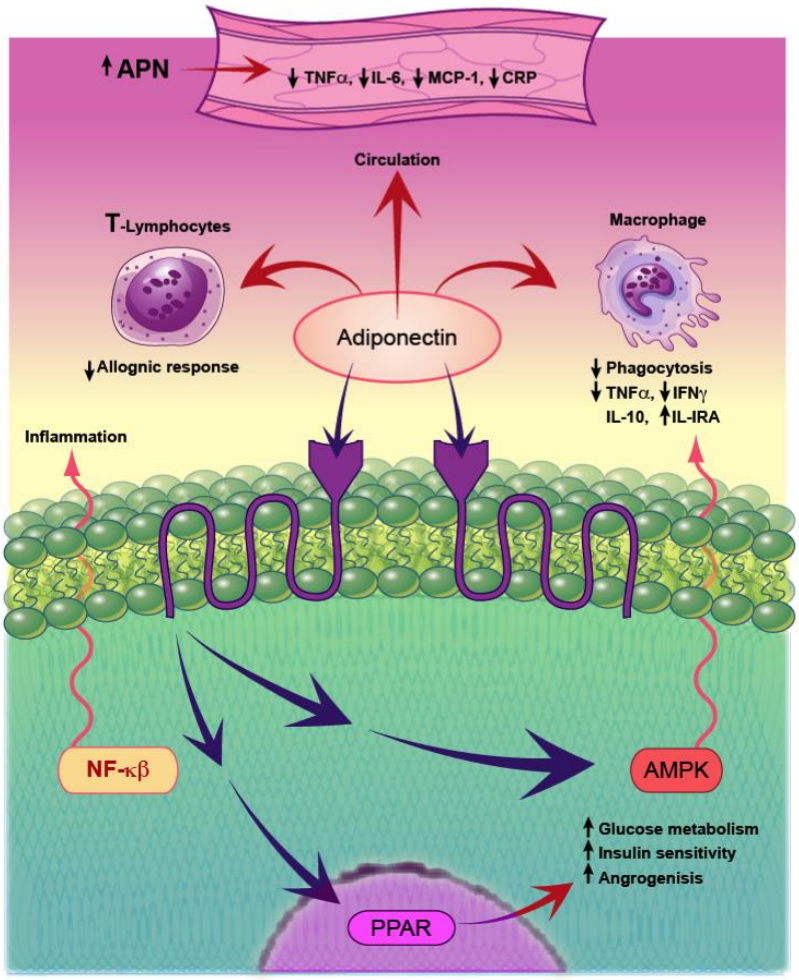

Figure 1: The role of adiponectin modulating immunity and the inflammatory response

In the context of obesity, the function of adiponectin as a strong anti-inflammatory modulator has been well established. Adiponectin exerts these anti-inflammatory effects by 1) downregulating chemokine and adhesion molecules, 2) altering lymphocyte and macrophage function, and 3) suppressing production of proinflammatory and upregulating production of anti-inflammatory cytokines.

Leptin, the first adipokine discovered in 1994, is widely known for its role in maintaining energy balance and the central regulation of satiety (143). Obesity (specifically increased adipocyte mass) leads to characteristic hyperleptinemia with subsequent leptin resistance (9,76). Leptin is a cellular mitogen, and also directly affects angiogenesis, the inflammatory profile, and immune cellular function. Leptin exerts downstream signaling primarily through the long form of its receptor (ObRl also known as Lep-Rb), which stimulates the Janus kinase 2/signal transducer and activator of transcription (JAK/STAT) pathway. This strategic position leads to downstream effects including increased angiogenesis (such as increased production of vascular endothelial growth factor [VEGF]) and decreased apoptosis. (8,10,18,120).

2. Acute Pancreatitis

Each year in the United States, over 240,000 patients are hospitalized with the primary diagnosis of acute pancreatitis, at a cost of over 2.3 billion dollars to the health care system (27). AP generates local inflammation as well as a

systemic inflammatory response that affects remote organ systems to variable degrees, resulting in a broad spectrum of disease severity. Importantly, despite the investment of a tremendous amount of basic and clinical research, no specific therapy has been shown to attenuate the clinical course of acute pancreatitis, and current treatment remains entirely supportive (127).

The central position of inflammatory cell infiltration and cytokine production in the development of acute pancreatitis is well established; many of the inflammatory changes observed in pancreatitis such as upregulation of chemoattractant and adhesion molecules, altered leukocyte function, and increased production of proinflammatory cytokines parallel changes seen in the generalized proinflammatory state induced by obesity, and thus offer a potentially attractive mechanistic link between these conditions.

Obesity and Clinical Acute Pancreatitis

A substantial amount of clinical evidence has confirmed obesity to have a significant negative impact on the course of acute pancreatitis. Autopsy studies performed nearly 50 years ago generated the observation that many patients with pancreatitis were obese (26). In 1985 Nordback and colleagues suggested that obesity was a risk factor for developing extensive pancreatic necrosis (90), and the seminal study of Lankisch and Schirren in 1990 showed that obesity was associated with the development of an increase in local complications of pancreatitis (69). Since the early 1990s, over a dozen published reports have evaluated the impact of obesity on the severity of acute pancreatitis (21,35,42,45,57-59,79 82,83,99,104,119,121,125). Nearly all of these studies have shown obesity to be associated with increased severity of pancreatitis as assessed by organ dysfunction. Additionally, many of these reports demonstrated that obese patients with pancreatitis have a significantly increased mortality rate relative to those with normal body mass (58,83). Martinez et al recently performed a well-controlled meta-analysis that included data from 739 patients (78). This analysis showed that both severity of disease (OR 2.9, CI 1.8-4.6) and mortality (OR 2.1, CI 1.0-4.8) were significantly higher in obese patients with pancreatitis. Thus, the collective weight of clinical evidence strongly supports the concept that obesity exacerbates acute pancreatitis.

Four clinical studies have examined adipokine levels in humans with acute pancreatitis; however, results from these studies are conflicting. Konturek and colleagues found serum leptin levels to be significantly elevated in 15 patients with mild acute pancreatitis as compared to healthy control patients matched for body mass index (BMI) (64). Similar results were reported by Schaffler et al, who studied 23 patients with pancreatitis and found that the circulating concentration of leptin and resistin correlated positively with severity of acute pancreatitis measured by radiological scoring scales (108). In this study, leptin also correlated positively with c-reactive protein (an inflammatory marker known to be elevated in pancreatitis), but not with a clinical pancreatitis severity score. These investigators also measured serum adiponectin concentrations, which were decreased in patients with more severe pancreatitis but did not reach statistical significance in most groups. Patients in this small study exhibited a broad range of obesity; however, no attempt was made to correlate BMI with either severity of pancreatitis or adipokine concentration.

In contrast to these studies, two other reports failed to find significant correlation of leptin with severity of pancreatitis. Duarte-Rojo et al measured serum leptin levels in 56 patients with acute pancreatitis (27% of whom had severe pancreatitis) (22). The average BMI in the mild and severe groups was similar, and no correlation existed between leptin concentration and severity of pancreatitis. Tukiainen and colleagues measured serum leptin and adiponectin levels in 24 patients with acute pancreatitis (126). Patients

were divided into those with mild and severe disease, and matched by age, sex, etiology, and BMI. No differences were observed in the average circulating level of leptin or adiponectin between patients with mild and severe pancreatitis. While it is somewhat difficult to compare the results of these small, heterogeneous studies, it is clear that the role of adipokines in the pathogenesis of human acute pancreatitis remains incompletely understood.

Obesity and Experimental Acute Pancreatitis

A few studies have evaluated the role of obesity on acute pancreatitis in experimental animal models. In one study of pancreatitis in an obese animal model, Swedish investigators studied three groups of rats: lean control animals, genetically obese (Zucker fa/fa), and animals in which obesity was generated by high fat diet (110). Pancreatits was induced by retrograde infusion of sodium taurocholate into the pancreatic duct. Genetically obese rats had significantly increased mortality, while animals with diet-induced obesity displayed more severe histologic pancreatitis relative to lean animals. These experiments confirmed the impact of obesity on severity of pancreatitis, but did not provide any mechanistic information.

Our laboratory performed experiments in lean and congenitally obese (Lep^{Ob} and Lep^{Db}) mice. Animals were subjected to acute pancreatitis generated by cerulein hyperstimulation. These experiments showed that both obese strains of mice sustained more severe pancreatitis than lean animals, and that severity of pancreatitis was inversely mirrored by circulating adiponectin concentration (147). Follow-up studies showed that 1) modest increases in adiponectin modulated the pancreatic chemokine and cytokine milieu in pancreatitis, and 2) central blockade of the cannabinoid-1 receptor increased circulating adiponectin concentration and significantly attenuated severity of pancreatitis in obese (Lep^{Db}) mice (146). These experiments confirmed the negative influence of obesity on the severity of pancreatitis, and strongly suggest that this effect is mediated at least in part by an alteration in the adipokine milieu (specifically a decrease in adiponectin).

Seven published studies have examined the role of adipokines in lean animal models of acute pancreatitis. Four reports are from a single Polish group, and focused on the proinflammatory adipokine leptin. These investigators have shown that circulating leptin is elevated in cerulein-induced pancreatitis, and that administration of exogenous leptin 1) decreases exocrine pancreatic secretion *in vitro* and *in vivo* and 2) attenuates the severity of acute pancreatitis induced by two discrete models using cerulein hyperstimulation and ischemia (53,54,64,134). Kerem et al confirmed the observation that circulating leptin concentration is elevated in lean rats subjected to pancreatitis by injection of cerulein or arginine (60). Yavuz et al also reported increased serum leptin levels in rats after pancreatitis was induced by ethanol injection into the common bile duct (140). Finally, Gultekin and colleagues demonstrated that exogenous leptin administration attenuates both pancreatic inflammation and lung injury in a rat model of cerulein-induced pancreatitis (43). Taken together, these studies suggest that 1) circulating leptin concentration is elevated in lean rats subjected to pancreatitis, and 2) though somewhat paradoxical, exogenous leptin administration appears to attenuate the severity of acute pancreatitis in animal models using lean rats.

Opportunities for Intervention in Pancreatitis

Both obesity and acute pancreatitis individually represent substantial health problems. Clinical studies have consistently identified obesity to be an independent risk factor for increased severity of acute pancreatitis. This combination results in a particularly devastating impact, as no specific therapy for pancreatitis currently exists. The concept that downregulating the anti-inflammatory adipokine adiponectin in obesity may potentiate

the severity of acute pancreatitis appears quite plausible; understanding the mechanisms by which obesity contributes to the severity of acute pancreatitis are critical to identify novel therapeutic and preventative treatments.

3. Pancreatic Adenocarcinoma

Pancreatic cancer is devastating: virtually every patient diagnosed with pancreatic cancer will die as a consequence of the disease (7,40,49,55). Advances in surgical technique and perioperative care have improved short term outcomes after resection of pancreatic cancer. Unfortunately, long-term survival after resection remains remarkably poor – fewer than 20% of patients will survive to 5 years (1,49,88). These dismal results clearly reflect aggressive (and poorly understood) tumor biology, highlighting the desperate need to develop novel therapeutic approaches.

Viewed in this context, the platform of obesity provides an opportunity to evaluate cancer biology from a novel angle. The mechanisms by which obesity promotes pancreatic cancer are poorly understood. Study of pancreatic cancer in obesity therefore presents a golden opportunity to gain insight into unique aspects of pancreatic tumor biology, and thus identify novel targets for directed therapeutic intervention.

Epidemiology of Obesity-Related Pancreatic Adenocarcinoma

Numerous epidemiologic studies have evaluated the relationship between obesity and increased risk of developing pancreatic cancer. Together, the vast majority of these studies confirm a clear association between increasing obesity (generally measured as BMI) and increased risk of *developing* pancreatic cancer, similar to the influence of obesity on other solid organ malignancies (3,15,17,24,32,34,36,38,46,50,56,70-75,84-86, 91,95,102,105,106,111,112,117,118,138,142).

Clinical Observations of Obesity and Pancreatic Adenocarcinoma

One clinical study evaluated visceral fat - as measured by retrorenal fat measured on cross-sectional imaging and found that patients with increased visceral fat had nearly twofold increased incidence of any complication of pancreatic resection. A second study evaluated 240 patients having pancreatoduodenectomy for pancreatic adenocarcinoma. In this study, obesity was associated with increased operative time and blood loss, but not with increased overall complication rate or perioperative death (136).

Four clinical reports have specifically addressed the impact of obesity on long-term outcomes after pancreatic resection for adenocarcinoma. Results from these reports are heterogeneous. Fleming *et al* were the first to draw attention to the potential negative impact of obesity on long term survival of pancreatic cancer patients (31). Their report documented a nearly twofold increase in the risk of recurrence and disease-related death in a subset of patients (21% of their population) with BMI > 35. A second study included 306 resected pancreatic cancer patients, 22% of whom were obese (BMI > 30) (6). These patients had increased blood loss and perioperative complication rates; however, no difference in long-term survival (non-obese 12.6 months vs obese 11.3 months) between these groups. A third study reported outcomes in 795 patients undergoing pancreatoduodenectomy for cancer, 14% of whom were obese (124). Obese patients had increased blood loss and pancreatic fistula rates, but improved 5-year survival (22% vs 15% in non-obese patients).

A recent study from the Mayo Clinic included 586 pancreatic cancer patients resected over a 26 year period (61). Twenty-one percent of these patients were obese. Obesity correlated with increased operative duration and blood loss. Perioperative morbidity and mortality were similar in obese and non-obese patients, and no difference in long-term survival was seen.

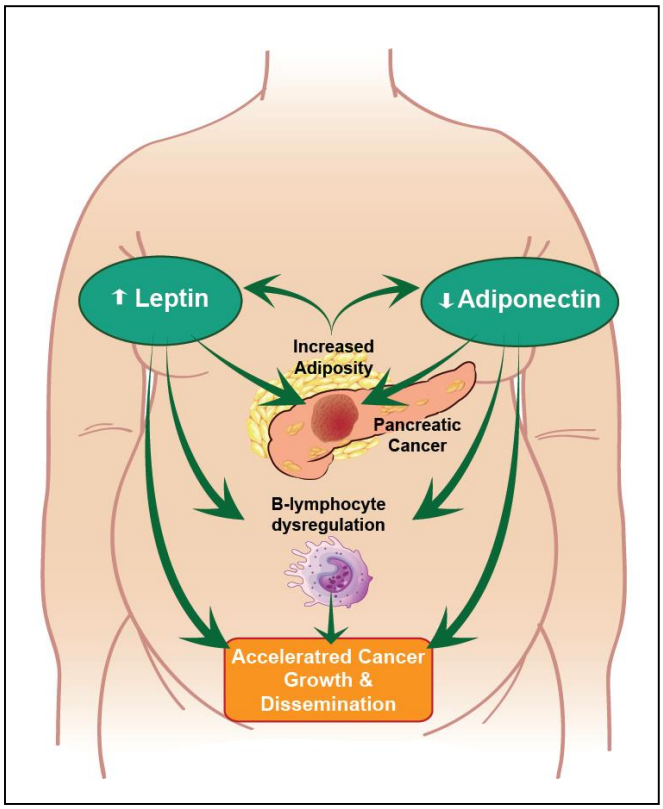

Figure 2: Mechanisms by which obesity may influence tumor growth

These studies highlight several challenges associated with obesity research. Firstly, BMI, while relatively easy to calculate and follow, is a very blunt instrument with which to measure the true effects of obesity. Although BMI is well accepted as an obesity measurement, it results in somewhat artificial segregation. Better measures may include volumetric analysis of visceral fat (66). For example, a small pilot study by Balentine et al suggested that increased intraabdominal fat correlated with poorer survival in pancreatic cancer, irrespective of BMI (4). Along these lines, our group showed a correlation between increased intrapancreatic adipocyte volume at the cut neck margin and poor long term survival (81).

Basic Mechanisms in Obesity Related Cancer

Broadly speaking, obesity may impact tumor growth at multiple different levels: systemically, by influencing the inflammatory milieu and immune response; locally (i.e. the peri-pancreatic and/or retroperitoneal adipocyte mass) by paracrine hormonal/inflammatory mediator production; and directly at the tumor level via intratumoral adipocytes within the microenvironment **(Figure 2)**.

Leptin, Adiponectin, and Cancer

Leptin receptors have been identified in numerous cancer tissues and cell lines, including breast, colon, esophageal, genitourinary, endocrine, and lymphoma/leukemia (37,52). Our group has documented leptin receptor presence on murine pancreatic cancer cells. *In vitro* studies have generally shown leptin to be mitogenic in cancer cell systems, including breast, colon, ovarian, lung, prostate and esophageal (37). However, some inconsistencies exist. For example, exogenous leptin administration did not affect adrenal cancer cells in culture (41), and while leptin promoted the growth of hepatocellular cancer cells *in vitro*, exogenous leptin suppressed growth of this tumor in nude mice (25,133).

Epidemiologic studies have shown an association between increased serum leptin and increased tumor growth in a wide range of cancers including breast, colorectal, ovarian, and genitourinary (39). Though not all epidemiologic studies have been uniformly conclusive, these clinical data largely support the relationship between elevated leptin concentration and an increased incidence of cancer.

Adiponectin receptors have been identified on a wide variety of cancer cell lines and human tumors, including breast, colon, gastric, endometrial, neuroblastoma, and hepatocellular carcinoma. We and others have documented adiponectin receptor presence in murine pancreatic cancer cells. *In vitro* studies have shown that adiponectin suppresses the growth of leukemia, breast, prostate, and hepatocellular carcinoma (14,65,132,141). In contrast, exogenous adiponectin stimulated proliferation of colonic HT29 epithelial cells (94). Far fewer *in vivo* studies have been reported; however, increased adiponectin (either by exogenous administration or by adenovirus upregulation) has decreased mammary tumorigenesis, fibrosarcoma, and hepatocellular carcinoma (11,65,77). On the other hand, adiponectin transgenic mice did not show reduced susceptibility to developing carcinogen-stimulated colon cancer (23). Interesting recent studies have explored the potential interaction between adiponectin and leptin: adiponectin has been shown to inhibit leptin-stimulated proliferation of esophageal, colon, and hepatocellular cancer cell lines (29,89,93) .

Clinical and epidemiologic studies have shown a strong and consistent inverse association between adiponectin and cancer development, including breast, endometrial, prostate, gastric, colon, and leukemia (39). Thus, while fewer data regarding adiponectin and cancer are available, the majority of clinical and experimental studies support the relationship between decreased adiponectin and increased carcinogenesis.

Leptin and Adiponectin in Pancreatic Adenocarcinoma

Several reports have evaluated leptin and adiponectin in pancreatic cancer. Brown *et al* were the first to measure preoperative serum leptin concentration in PDAC patients (12). Two other smaller studies showed decreased serum leptin concentration in pancreatic cancer patients relative to control patients (20,103). Patients in both of these studies were lean, which may explain why these small clinical studies conflict with the majority of other reports of leptin in cancer.

In experimental studies addressing leptin's effect on pancreatic cancer growth, exogenous leptin (in subphysiological doses) decreased the growth of two human pancreatic cancer cell lines (114). In contrast, our group has shown increased pancreatic cancer growth in obese mice that are hyperleptinemic (Lep^{Db} and diet-induced obese mice) as well as in those without leptin (Lep^{Ob}) (135,148). These conflicting findings highlight the need to study the isolated effects of leptin on pancreatic cancer. Leptin receptors are present in human pancreatic cancers; in preliminary studies, we have documented the presence of leptin receptor mRNA in murine pancreatic cancers.

Clinical studies evaluating adiponectin in pancreatic cancer have generated inconsistent data. Two studies reported increased serum adiponectin concentration in patients with pancreatic cancer relative to controls (19,20). All patients in these studies were lean, and at least half had jaundice and/or cholestasis (which significantly affects adiponectin measurement). Another small study reported no difference in circulating adiponectin concentration between pancreatic cancer patients and controls (10). The largest study of adiponectin in pancreatic cancer patients documented an inverse relationship between circulating adiponectin and risk of pancreatic cancer (116).

In experimental studies, our group found a significant negative correlation between circulating adiponectin and proliferation of murine pancreatic cancers in a congenital obesity model, as well as a significant negative correlation between adiponectin and tumor weight in a diet-induced obesity model (135,148). Adiponectin receptors are present in human pancreatic cancer (20); we have also documented the presence of AdipoR1 and AdipoR2 in murine pancreas (130) as well as in murine pancreatic cancer cell lines.

From currently available data, elevated leptin *in general* is associated with increased tumorigenesis in clinical studies and is mitogenic in *in vitro* cancer systems, while decreased adiponectin *in general* is associated with increased tumorigenesis in clinical studies and adiponectin administration attenuates cancer growth *in vitro*.

Other Mechanisms Linking Obesity and Cancer

In addition to altered adipokine milieu, several other mechanisms offer attractive links between obesity and cancer. These mechanisms include adipocyte production of growth factors and proangiogenic factors, mitochondrial dysfunction related to oxidation-reduction potential, changes in the inflammatory profile, steroid hormone imbalance, obesity-regulated immune cell modulation, and dysregulation of the insulin axis (16,129). Hyperinsulinemia and alteration of insulin-like growth factors present in the obese state may either interact with or obscure other direct and indirect effects of adipokines.

4. Conclusions

Obesity clearly exerts a negative effect on patients with acute pancreatitis and pancreatic cancer. Strong epidemiologic data show that obesity is associated with increased development of pancreatic cancer. The mechanisms modulating the effects of obesity on pancreatic disease are partly defined, but offer exciting paths for study, and an opportunity to discover much needed therapy for these devastating problems.

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