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Chapter 4

Linking Obesity and Pancreatic Cancer

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1. Introduction

Cancer of the pancreas is the tenth most common form of cancer in the United States and the fourth leading cause of cancer-related death with a stunningly low 5-year survival rate of less that 6% [1-4]. Although there are genetic links with pancreatic cancer (10-15% of patients diagnosed will have a family history) [5], chronic pancreatitis [6], cigarette smoking and smokeless tobacco [7, 8], obesity [9-11], and type 2 diabetes mellitus (T2DM) [12-14] are the strongest environmental risk factors linked to this malignancy. Recently high fructose corn syrup (HFCS) consumption which also contributes to obesity, T2DM, and non-alcoholic fatty liver disease (NAFLD), has also been directly linked to pancreatic cancer [15]. The development of the industrial age and subsequent loss of the "hunter-gatherer" life-style has resulted in a world-wide epidemic of obesity and its associated chronic diseases including: atherosclerotic heart disease, stroke, diabetes, and multiple obesity-associated malignancies including cancer of the pancreas. Epidemiologic studies have demonstrated that as underdeveloped countries progress into industrialized economies and life-styles change (especially consumption of high density fat/carbohydrate diets coupled with decreased physical activity), the prevalence of obesity and obesity-related chronic diseases increases. The direct link between obesity, chronic inflammation, and oncogenesis is becoming increasingly more appreciated and the underlying cellular mechanisms involved this process are currently intensively being investigated and reviewed [16, 17]. In addition to the direct role of obesity in oncogenesis, obese individuals also demonstrate worse outcomes and shorter cancer survival compared to persons with normal body mass indexes (BMIs) [16]. These observations suggest that the abnormal hormonal and inflammatory milieu of obesity is directly involved in oncogenesis, promotes tumor growth, spread, and metastasis while possibly also increasing resistance to therapeutic intervention [16]. This chapter is meant to review the links between obesity, abnormal adipose tissue function, induction of abnormal hormonal and chronic inflammatory signaling path-

ways involved pancreatic cancer origin, growth, spread, and resistance to treatment. Our research efforts have been focused on the role of pathologic expression of toll like receptors (TLRs) in this process which links increasing visceral obesity to these processes.

2. Genetic linkage to pancreatic cancer

Family aggregation of pancreatic cancers suggests a genetic linkage and several important pancreatic cancer susceptibility genes have been identified including high-penetrance genes: **BRCA2, PALB2, PRSS1, SPINK1, STK11** have recently been reviewed [5], and DNA miss-match repair genes. Genome-wide association studies (GWAS) are also finding single-gene polymorphisms (snps) that are also associated with increased risk for pancreatic cancer including: **ABO, 1q32.1, 13q22.1, CLPTM1/TERT, CFTR** [18, 19].

Chronic pancreatitis is the strongest independent risk factor for cancer of the pancreas and there are environmentally induced forms as well as rare inherited forms. Autosomal dominant mutations of the cationic trypsinogen gene **PRSS1** causes a hereditary form of chronic pancreatitis [20] while an autosomal recessive defect in the serine protease inhibitor gene **SPINK1** also causes hereditary pancreatitis [21]. These familial forms of chronic pancreatitis exhibit the greatest risk for pancreatic cancer (50-fold increase compared to the general population) and these individuals also experience the longest duration of chronic pancreatitis as well. As life expectancy from cystic fibrosis (CF) has increased from childhood into adulthood, individuals with the cystic fibrosis transmembrane conductance regulator (**CFTR**) gene now exhibit a 5-fold increased risk for pancreatic cancer from their early onset exocrine pancreatic disease and chronic pancreatitis [22, 23]. These are the major genes associated with risk for pancreatic cancer to date and most investigators anticipate that gene-gene and gene-environmental interactions coupled with the chronic inflammation are cooperatively involved in the pathogenesis of such complex cancers.

3. Environmental causes of chronic pancreatitis

Patients with chronic pancreatitis from any cause are at increased risk for pancreatic cancer with severity and duration of chronic pancreatitis (>20 years), age of the patient, and concomitant tobacco use being the major associated co-factors. Although alcohol abuse is causally linked to the development of chronic pancreatitis, interestingly it does not appear to be an independent risk factor for pancreatic cancer which has been confirmed by multiple recent epidemiologic met-analysis studies [24, 25]. **Cigarette smoke contains numerous carcinogenic compounds** including nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone **(NNK) [26]**. One of the most well-known features of NNK is the ability of its metabolites to bind to DNA and induce activating point mutations in the RAS gene [26]. Nicotine itself has also been shown to stimulate Src kinase activity which facilitates the induction of the inhibitor of differentiation-1 (Id1) transcription factor which promotes pancreatic tumor growth, meta-

stasis, and resistance to chemotherapeutics. Cigarette smoking also increases the risk for T2DM by inducing insulin resistance as well. Finally, as will be reviewed below, increasing BMI and obesity are also clearly risk factors for the development of hyperlipidemia, T2DM, chronic pancreatitis, and a 2-fold higher prevalence of pancreatic cancer.

4. Epidemiology of obesity, T2DM, and pancreatic cancer

There are multiple epidemiologic studies in the US and world-wide linking the epidemic of obesity and higher BMI to increa`sed risk for multiple malignancies including carcinoma of the pancreas [10, 27]. The American Cancer Society calculates that of the 1.5 million new cancer cases diagnosed each year, at least 20% are due to obesity [2]. The risk of pancreatic cancer in both men and women is increased in those who have a BMI > 25 but is most pronounced in those with a BMI of 35 or greater [11, 28]. The risk has been shown to increase by 10 per cent for every five-point increase in BMI. The strongest environmental risk factors related to pancreatic cancer as stated previously are cigarette smoking [8] and obesity [9]; both of which are also linked to inducing chronic inflammation, insulin resistance and T2DM [14]. As stated previously, individuals with T2DM are also twice as likely to develop acute pancreatitis and pancreatic cancer compared to non-diabetics [9, 10]. Studies looking at the components of diet and pancreatic cancer link increased risk with consumption of high fat diets, processed and/or organ meats, the glycemic index of food, and recently high-fructose corn syrup (HFCS) as important factors contributing to obesity, T2DM and risk for carcinoma of the pancreas [15]. As many as 40-50 % of patients with chronic pancreatitis will develop diabetes mellitus (DM) from the chronic destruction of beta cell function as well (insulin deficiency rather than the hyperinsulinemia discussed later). Furthermore, 40% of patients with carcinoma of the pancreas develop insulin deficiency from tumor replacement of beta cells and the DM often precedes the diagnosis of the cancer.

In contrast, there is a reciprocal relationship between the amount of exercise and risk for obesity, T2DM, and pancreatic cancer. Exercise alone burns calories and reduces the risk and/or severity of obesity, reduces insulin resistance, and promotes the production of anti-inflammatory cytokines which counter all of the proinflammatory and oncogenic processes which are discussed below [10].

5. Molecular pathways linking obesity, inflammation, diabetes, and pancreatic cancer

When caloric intake exceeds normal metabolic demand there is a need to store this excess energy and that is the principle function of the adipocyte. Adipose tissue however, is more than just a storage depot. Adipose tissue (especially **visceral fat**) is composed of multiple cell types (adipocytes, pre-adipocytes, macrophages, fibroblasts, and blood vessels), and is now recognized as a significant endocrine organ that expresses and secretes multiple hormones

(leptin, adiponectin, resistin), inflammatory cytokines (TNF-α, IL-6, and IFN-β), components of complement, plasminogen activator inhibitor-1 (PAI-1), vascular endothelial growth factor (VEGF) and other proteins such as monocyte chemoattractant protein (MCP-1). These adipose tissue-derived factors (Figure 1) are now thought to contribute dramatically to the induction of chronic inflammation which is expressed as insulin resistance [29], hyperinsulinemia, T2DM, hyperlipidemia, hypertension, and atherosclerosis [30], and also contributing to the oncogenesis of many solid tumors [11, 16]. Visceral obesity is the fat depot most closely associated with the production of these substances and the subsequent development of insulin resistance, T2DM, and pancreatic cancer oncogenesis.

5.1. Dietary contributions

a. High Fat Diets (HFDs) and Excess Free Fatty Acids (FFAs):

Dietary fats (triglycerides, glycerol, and FFAs) are directly absorbed from the small intestine as chylomicrons into the thoracic duct into the subclavian vein and then into the general circulation. Chylomicrons are taken up by adipocytes and hepatocytes [31]. However, once the adipocyte storage capacity is exceeded, excess TG's and FFA's stimulate adipogenesis and are deposited ectopically into the liver where these excess fats accumulate in small vacuoles within hepatocytes which is the first stage of fatty liver disease (steatosis) [32, 33]. There is also increased *de novo* hepatic lipogenesis with consequent endogenous over-production of triglycerides (TGs) and free fatty acids (FFAs). Excess fats are also deposited in skeletal muscle and other insulin target tissues (even beta cells of pancreas) where they initiate acute inflammatory processes (lipotoxicity) with the activation of multiple inflammatory cytokines [16]. Inflammatory cytokines in turn, directly contribute to the induction of insulin resistance through down regulation of the insulin receptor (IR) and post-receptor signaling pathways in insulin target tissues [33]. In the liver, the ectopic dietary fat also initiates an inflammatory response (steatohepatitis) which contributes to the development of non-alcoholic fatty liver disease (NAFLD) [33].

Within visceral fat cells themselves, FFAs (palmitate, etc.) directly induce the release of inflammatory cytokines [16] and also trigger the pathologic signaling of toll-like receptors (TLRs); activation of TLR4, in particular, increases additional inflammatory cytokine production, contributing to the initiation of insulin resistance [34] and adipogenesis, further increasing adipocyte mass, and the chronic inflammatory state now associated with obesity, T2DM, and oncogenesis.

b. High Fructose Corn Syrup (HFCS):

Fructose is a dietary carbohydrate normally derived from plant sources (tree and vine fruits, flowers, berries, and most root vegetables) which is much sweeter than glucose or sucrose. It is commonly used commercially in prepared foods due to its sweetness, effects on prepared food texture, and browning of baked foods. Commercially it is derived from sugar cane, sugar beets, and corn. HFCS is a mixture of glucose and fructose as monosaccharaides and as a food supplement it is now being vilified for its role in the obesity epidemic as well as induction of insulin resistance, T2DM and non-alcoholic fatty liver disease (NAFLD) [35-38]. NAFLD is

now the leading cause of cirrhosis of the liver and primary hepatocellular cancer. Diets high in HFCS have also been linked directly to increased risk for pancreatic cancer [39]. Mechanisms by which HFCS induces insulin resistance are thought to be due to its unique metabolism in the liver via pathways identical to alcohol. Fructose binds to only one of the glucose transporters (GLUT 5) which is present only in enterocytes of the intestine and in the liver. Thus, although it is selectively concentrated in the liver, fructose cannot be utilized as a carbohydrate for energy in any other cell or organ of the body. Acutely, fructose ingestion results in the shunting of fructose-1-phosphate into dihydroxyacetone-phosphate and glyceraldehyde which enters the TCA cycle from pyruvate and citrate to excessively increase *de novo* hepatic lipogenesis and the over-production of TGs and FFAs [40]. Fructose-1-phosphate also directly induces janus kinase-1 (**JNK-1**) signaling, increasing serine phosphorylation of insulin receptor substrate-1 (**IRS-1**) in the liver and preventing normal insulin-stimulated tyrosine phosphorylation of IRS-1 [41]. TG and FFAs derived from HFCS intake also induce insulin resistance in the liver as the FFAs precipitate in hepatocytes (lipid droplet accumulation), also stimulating excessive TLR4 signaling and further amplification of multiple inflammatory cytokine pathways. Dihydroxyacetone-phosphate and glyceraldehyde are also both directly hepatotoxic while the excessive accumulation of lipid droplets in the liver induces steatosis further amplifying inflammatory cytokine release. All of these processes are thought to contribute to progressive development of hepatic fibrosis, cirrhosis, and primary hepatic cancer. Elevated TGs and FFAs produced by the liver or which cannot be cleared from the portal vein by the liver accumulate in the peripheral circulation, exerting similar effects on the insulin receptor signaling in other target tissues such as adipose tissue, skeletal muscle, and the exocrine pancreas [40].

With regard to pancreatic cancer, there is increasing evidence of a specific dose-dependent linkage between HFCS intake and its occurrence and this risk is independent of obesity or BMI [15]. Furthermore, fructose directly stimulates increased nucleic acid synthesis through the pentose phosphate pathway (catalyzed by transketolase) which is necessary for proliferation of malignant cells and consumption of HFCS is now linked both to oncogenesis as well as tumor spread and metastasis [15].

c. Carcinogens in Foods:

High intake of processed meats containing heterocyclic amines and benzo (a) pyrines or have been prepared at high temperatures (fried or grilled) have been linked to pancreatic cancer [42] as have other foods containing aflatoxins [43] and other mutagens, however their link to pancreatic cancer are fairly weak at this time.

5.2. Molecular pathways triggered by dietary constituents

a. Adipocyte-Derived Inflammatory Proteins:

Inflammatory cytokines (adipokines) such as **TNF-α, IL-6, IL8, VEGF, and IFN-β** have been shown to be elevated in states of visceral obesity [16], as well as acute and chronic pancreatitis, and pancreatic cancer [11]. Visceral adipocytes/macrophages are major sources of the obesity-associated cytokines which are thought to promote insulin resistance [29] (see below) as well

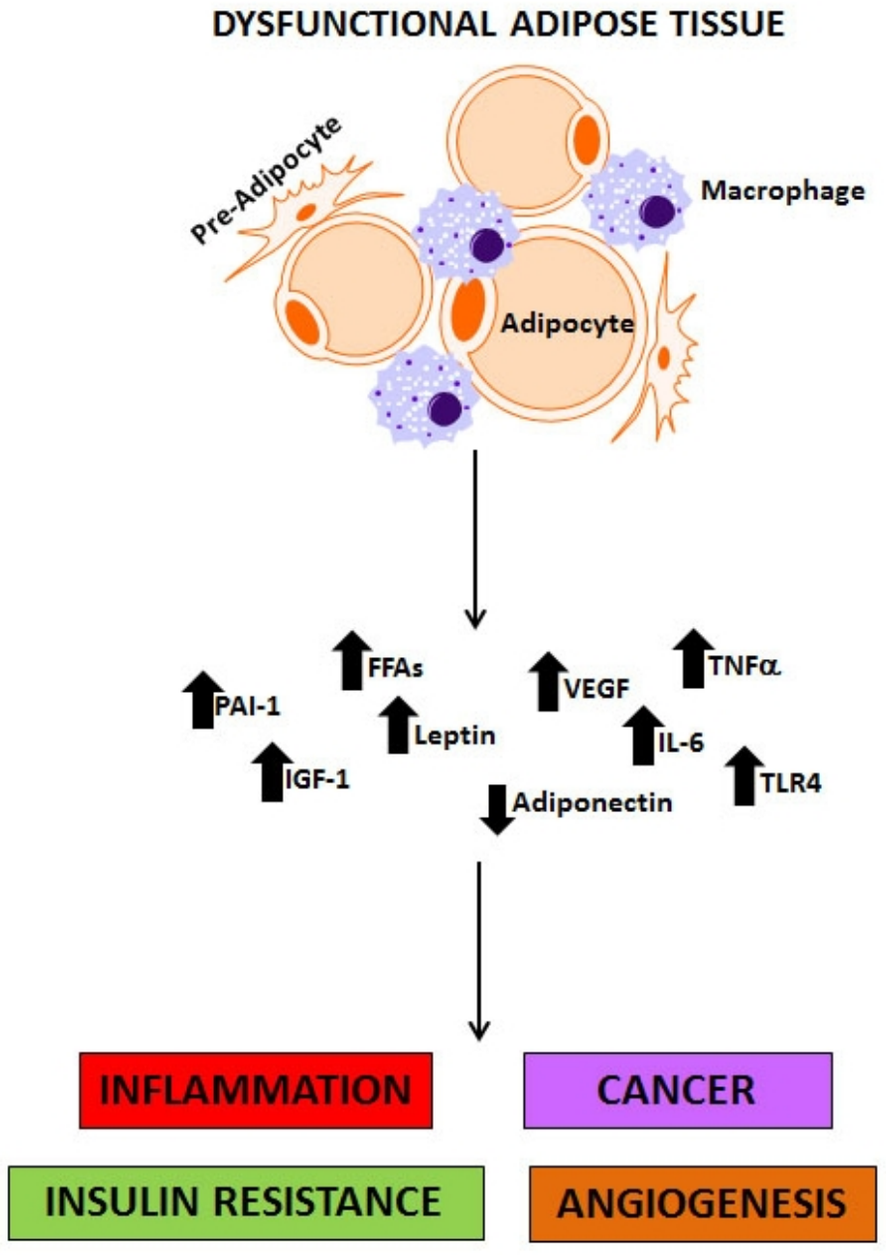

Figure 1. The role of dysfunctional adipose tissue in obesity. Dysfunctional adipose tissue is a critical source of molecules that mediate inflammation, cancer, insulin resistance and angiogenesis. PAI-1 (plasminogen activator inhibitor-1); FFAs (free fatty acids); IGF-1 (insulin-like growth factor 1); VEGF (vascular endothelial growth factor); IL-6 (interleukin 6); TNF-α (tumor necrosis factor alpha); TLR4 (toll-like receptor 4).

as directly contribute to oncogenesis via several pathways [16] including other growth factor receptors, cytokine receptors, or non-receptor tyrosine kinases. Each of these pathways can increase Janus kinase (JAK)/signal transduction and activator of transcription Signal Transducer and Activator of Transcription (STATs) of which **STAT3** [44, 45] is directly linked to cancer of the pancreas. Both of these pathways can stimulate cellular proliferation—transformation through (1) up-regulation of genes encoding cell cycle regulators (cyclins D1/D2, c-Myc), (2) increasing the probability of mutation, (e.g., cellular proto-oncogenes, DNA, and

cellular repair mechanisms), (3) inhibition of apoptosis (*Bcl-xL, Mcl-1*), (4) decreased cellular adhesion, and/or (5) stimulation of angiogenesis (VEGF) [46].

Leptin is also secreted by adipocytes and plays a key role in regulating metabolism and appetite. Leptin is known as the satiety hormone however serum leptin levels are elevated in obesity due to central leptin receptor resistance (by mechanisms similar to insulin discussed below). Leptin has mitogenic actions in many cancer cell lines which appear to be via mitogen-activated-protein-kinase (**MAPK**) mediated pathways; however in certain pancreatic cancer cell lines it inhibits growth [47] so its role in this cancer is unclear at present [48, 49].

Adiponectin is exclusively secreted by adipocytes and has both anti-inflammatory and insulin-sensitizing effects. Known as the "good adipokine" serum levels of leptin are inversely related to BMI and levels are reduced obese patients and in many cancers. High levels of adiponectin are inversely related to the incidence of pancreatic cancer [49].

PAI-1 is a serine protease inhibitor produced by adipocytes and stromal cells in visceral fat, is associated with tumor cell invasion, metastasis, and angiogenesis of many malignancies, and over-expression of PAI-1 has been demonstrated in many obesity-related tumors suggesting it contributes to the spread of malignancies [50]. Interestingly, high expression of the plasminogen activator inhibitor-2 (PAI-2) was a predictor of improved survival in patients with pancreatic adenocarcinoma [51].

VEGF is another adipocyte-derived polypeptide that has been implicated in cancer growth, shown to be over-expressed in many pancreatic cancers, and its expression in these tumors is linked to poorer survival [52, 53].

b. Insulin Resistance, Hyperinsulinemia, and Increased Insulin/IGF-1 Receptor Signaling Pathways

The FFA's and inflammatory cytokines produced by visceral obesity discussed earlier directly induce insulin resistance at the insulin receptor (IR) level [34, 54] resulting in compensatory beta cell insulin secretion (hyperinsulinemia) in an attempt to maintain euglycemia. The hyperinsulinemia becomes a self-perpetuating vicious cycle, in turn, as it directly contributes to insulin resistance by down-regulating its own receptor. Insulin resistance can originate anywhere in the insulin-action cascade; from a direct reduction in IR number or affinity, to reduced phosphorylation/activation of the insulin receptor itself, to down-regulation of the intracellular protein-kinase cascade normally triggered by insulin action following interaction with the IR (post-receptor signaling) [55]. Over-stimulation of the IR by hyperinsulinemia itself results in high levels of **STAT3** activation, which then up-regulates suppressors of cytokine signaling-3 (***socs-3***); which in turn, inhibits post-receptor insulin signaling as a negative "feedback" inhibitory mechanism, thereby down-regulating its own receptor system [56]. We have shown that excessive TLR4 signaling and inflammatory cytokine release up-regulates *socs-3* which contributes to insulin resistance [34]. Overall decreased insulin signaling then leads to decreased activation of GLUT4 transporters and decreased insulin-stimulated suppression of hepatic gluconeogenesis and glucose uptake into peripheral target tissues such as adipocytes and skeletal muscle which leads to the development of T2DM. Although IR-mediated pathways associated with carbohydrate and fat metabolism are down-regulated,

other signaling pathways are not suppressed but rather continuously stimulated by insulin resulting in activation of the Ras/Raf/mitogen-activated-protein-kinase (**MAPK**) system and **mTOR** pathways which are known to promote abnormal cell growth and proliferation [57, 58]. Thus, in states of obesity and FFA/TLR4/cytokine-mediated insulin resistance, the principle functions of insulin action via the IR (glucose transport and suppression of gluconeogenesis) are impaired while insulin-stimulated abnormal cell growth and proliferation in target tissues continues [58]. Secondly, hyperinsulinemia induces the synthesis of insulin-like growth factor-1 (**IGF-1**) in liver and the high serum levels of free IGF-1 also results in overstimulation of its own receptor (IGF-1R). Excess IGF-1R signaling also stimulates abnormal cell proliferation through the same downstream signaling networks which are being chronically stimulated by insulin; including the phosphatidylinositol 3-kinase **(PI3-K)-AKT** system [58]. Thus obesity induced insulin resistance results in excess insulin and IGF-1 promotion of abnormal cell growth and proliferation in multiple organ systems. Expression of IGF-1 receptors has also been demonstrated in multiple malignant tumors including pancreatic cancer, and IGF-1 contributes to cell migration and invasion in some human pancreatic carcinomas.

c. Hyperglycemia Induces Pancreatic Cancer Epidermal Growth Factor Expression

As we have previously discussed in this chapter, diabetes is associated with an increased risk of pancreatic cancer by a variety of cytokine and hormone receptor signaling pathways and that large numbers of patients with pancreatic cancer develop diabetes and elevated glucoses. The direct effect of hyperglycemia on oncogenesis, pancreatic cancer growth and spread is of interest as well. Epidemiologic studies have demonstrated that glucose control in patients with pancreatic cancer results in improved survival, suggesting that high glucose levels might directly promote tumor growth and progression [59]. Recent *in vitro* cell culture studies have demonstrated that glucose in a dose-dependent manner promotes different pancreatic cancer cell line growth and perineural invasion through the regulation of expression of glial cell line-derived neurotropic factor (GDNF) and epidermal growth factor (EGF) via increased epidermal growth factor receptor (EGFR) transactivation [60]. These observations support intensive glucose control as a potential target for improving patient survival in pancreatic cancer.

6. Obesity, toll-like receptors, and pancreatic oncogenesis

Toll-Like Receptors (**TLRs**) are pathogen recognition receptors (PRRs) critical for the activation of the innate and adaptive immune responses to foreign pathogens. Functional TLRs are not only expressed in immune cells but also in many non-immune cells [61]. Their activation, signaling, and proinflammatory responses have been shown to be mediators of multiple inflammatory and autoimmune diseases, as well as, contribute to oncogenesis, tumor growth and metastasis. Pathologic signaling of multiple TLRs have been implicated in many cancers including; melanoma, breast, prostate cancer, colorectal, lung, cervical, liver, and pancreatic cancer [62-64]. Obesity and T2DM are associated with an increased risk for many of these same malignancies; especially pancreatic cancer. FFA's are capable of activating TLR4 signaling in

adipocytes which stimulates adipocyte differentiation, high fat diet (HFD)-mediated induction of visceral obesity, TLR4-mediated cytokine signaling, insulin resistance, and glucose intolerance [34, 65]. This in turn stimulates insulin/IGF-1 signaling pathways which also promote tumor growth. Fructose also stimulates abnormal TLR4 signaling [36] and as mentioned earlier, HFCS diets are associated with induction of visceral obesity, T2DM, chronic pancreatitis, and cancer of the pancreas as well. Since both FFA's and fructose are potent ligands for TLR4 and both are present in high concentrations in the diets of developed countries it is logical that they could promote pancreatic oncogenesis via TLR mediated pathways to be described. Finally, as just mentioned hyperglycemia in the form of glucose intolerance and overt T2DM also stimulates abnormal TLR4 signaling [66] as well as EGFR transactivation in pancreatic tissue in a glucose dependent manner thus also serving as a ligand to promote tumor growth and spread.

Chronic inflammation has been shown to be an important risk factor for the onset and progression of multiple cancers, including pancreatic cancer [67-72] [72-75]. Chronic inflammation is thought to induce malignant transformation via activation of oncogenes, induction of immunosuppression, and inhibition of tumor suppressor genes and lymphocytes. Pathologic activation of TLRs play a critical role in the inflammatory response induced by high fat diets and HFCS by inducing the production of multiple pro-inflammatory cytokines and they have been shown to be important for the induction, proliferation, survival, metastasis, and escape from immune surveillance of many of these cancers as well [70, 76]. Some of the most important TLR-induced cytokines implicated in cancer include **TNF-α, IL-1, IL-6, IL-8, IL-10 and IL-23.** Proinflammatory cytokine production then leads to the activation of many tumor promoting transcription factors and anti-apoptotic genes. Nuclear factor kappa beta **(NF-κB**) and **signal** transducer and activator of transcription 3 (**STAT3**) are two of the most well studied oncogenic transcription factors.

7. Pathologic toll-like receptor signaling, pancreatic cancer growth, and resistance to therapy

We have previously described the relationship between obesity and pancreatic cancer risk as well as the direct correlation between increasing BMI and hyperglycemia to lower responses to treatment and over-all worse outcomes in this all too common disease. Obesity-induced TLR activation of NF-κB and STAT3 signaling pathways are major mediators of this process in multiple cancers including pancreatic cancer. NF-κB and STAT3 are activated by a variety of similar stimuli (stressors, cytokines, etc.) and both control expression of proliferation-enhancing, anti-apoptotic, angiogenic, and immune-modulating genes; however they are regulated by entirely different signaling mechanisms. NF-κB's pro-inflammatory cytokine receptors such as; **TNF-α** and **IL-1** [77-80] promote not only tumor transformation, but also proliferation, angiogenesis, invasion, metastasis, and chemo/radio resistance [81-89]. STAT3 activation by TLR-mediated cytokines also activates the **IL-6 family** (IL-6, IL-11, IL-27, etc.), **IL-10 family** (IL-10, IL-22, IL-19, IL-20), and the epidermal growth factor (**EGF**) family (VEGF, IL-21, IL-23, HGF) of growth factors which also stimulate tumor transformation, growth and

resistance to therapy. NF-κB and STAT3 activate anti-apoptotic genes such as Bcl-xL, Bcl-2, and c-IAP2 [90-92] and also interact and mediate crosstalk between tumor cells and inflammatory cells within the tumor microenvironment to promote the development and progression of multiple types of human cancers including but not limited to pancreatic, colon, gastric, skin, head and neck, and liver cancers [44, 90, 93-96]. Finally, Wnt5a a member of the Wnt family has also been implicated in carcinogenesis and inflammation. Non-canonical Wnt5a activates β-catenin-independent pathways important for cell migration and polarity. Wnt5a has been found in tissue samples of pancreatic adenocarcinomas [97] and is highly expressed in advanced pancreatic cancer [98]. Recently, a TLR / IL-6 / STAT3 / Wnt5a signaling loop was described [62, 99].

8. TLRs as a potential therapeutic target

Several recent studies have evaluated the potential therapeutic use of TLR activators and inhibitors in multiple cancer models. The theory for activation of TLR signaling pathways in a tumor environment is that it would possibly induce tumor cell apoptosis or inhibit the production of various factors described in this review that control tumor growth. In addition, it induction of TLR signaling could elicit an antitumor immune response that could lead to tumor cell destruction by the host's immune system. Treatment with TLR agonists have shown to induce an antitumor response by enhancing dendritic cell (DC) vaccination or T cell adoptive therapies. A recent study reported that the use of TLR agonists such as poly(I:C) or CpG combined with adoptive transfer immunotherapy directly to a B16F10 melanoma model inhibited tumor growth [100]. Also, in a mouse breast xenograft model, the antitumor effect of the TLR3 activator was shown to be dependent on the expression of TLR3 expression in tumor cells. This was further validated in humans where treatment with dsRNA improved outcomes in patients harboring TLR3-positive breast tumors [101]. Similarly, CpG treatment via TLR9 activation induced tumor cell death in human neuroblastoma cells, and tumor-targeted delivery of this TLR9 agonist increased survival in a xenograft model of neuroblastoma [102].

In contrast, it has also been shown that TLR agonists can promote cancer cell survival and migration, and tumor progression. For example, TLR agonists have been shown to increase tumor viability and metastasis of human lung cancer (TLR7/8) [103] ; proliferation of human myeloma (TLR3) [104] ; adhesion and metastasis of human colorectal cancer (TLR4) [105] ; and migration of human glioblastoma (TLR4) or human breast cancer (TLR2) [106]. In regards to pancreatic cancer, TLR7 was recently reported not only be highly expressed in mouse and human pancreatic cancers, but ligation of TLR7 led to accelerated tumor progression through the STAT3 growth pathways previously discussed. Thus, there appears to be a double edged sword between reducing or promoting tumor growth using agonists based therapies for different TLRs.

On the other hand, the use of TLR antagonists has shown to be beneficial at inhibiting tumor growth in animal models in which the tumor microenvironment promotes survival and

metastasis via TLR signaling. TLR antagonists might also decrease the level of activation of stromal cells such as tumor-associated macrophages. Macrophages express an array of TLRs and are able to produce several growth factors via TLR signaling [107]. Moreover, abrogation of TLR-4 signaling in tumor-associated macrophages decrease tumor growth *in vivo* [108].

Our group demonstrated that in papillary thyroid carcinoma cells, IL-6, a TLR3 signaling product, activates STAT3, results in overexpression of **Wnt5a** which mediates tumor growth and spread [62]. Further, we demonstrated that phenylmethimazole (C10), a small molecule derivative of methimazole, blocked TLR3 signaling, and subsequent IL-6 production, STAT3 activation, Wnt5a overexpression, and subsequent growth and migration of papillary thyroid carcinoma cells [62]. Toll-like receptors were first implicated in the pathogenesis of pancreatic cancer in 2009. Our laboratory demonstrated that TLR3 and Wnt5a were coordinately constitutively expressed in a human pancreatic cell line (PANC-1), activation of signaling also played a key role in the regulation of pancreatic cancer growth and migration and that C10, inhibited its growth and migration both in vitro and *in vivo* [63]. Another study reported that activation of the TLR4 signaling pathway-increased invasiveness of pancreatic cancer cells while blockade of TLR4 signaling decreased invasive ability [109]. These studies were the first to implicate both TLR3 or TLR4 expression and signaling as playing a role in pancreatic tumor growth and migration and demonstrated that inhibition of TLR signaling pathways were potential therapeutic targets. Gemcitabine is currently the standard of care chemotherapeutic for pancreatic cancer; however, its efficacy is diminished due to toxicity and the chemoresistance of the tumors. Recently, another group combined TLR4/NF-κB antagonist with gemcitabine in an orthotopic model of pancreatic cancer and the combination therapy significantly delayed tumor growth and decreased tumor size compared to gemcitabine alone or the control groups. Thus, TLR antagonists, when combined with other chemotherapeutic agents may prove to be effective adjunctive therapies to suppress the inflammatory cytokine/growth factor microenvironment which contributes to the induction and/or support of tumor growth and progression and reduce the dose/toxicity of established agents.

9. Prevention of obesity associated pancreatic cancer

There is now compelling evidence that obesity, chronic inflammation, and the associated secretion of numerous inflammatory cytokines, hormones and growth factors described herein contribute both directly and indirectly to the increased risk for pancreatic cancer, more aggressive tumor growth, as well as poor response to therapeutic intervention. Thus, in addition to smoking cessation and moderation in alcohol consumption, life-style modification with exercise, maintenance of normal BMI's, consumption of higher amounts of fresh fruits and vegetables, less animal fat and processed foods; especially those fortified with HFCS are obvious recommendations. In addition, there is increasing evidence that other anti-inflammatory agents such as the non-steroidal anti-inflammatory drugs (NSAIDS) [110], the Statin lipid-lowering medications, and T2DM medications such as the thiazolidinediones (TZD's) [111] and metformin [112, 113] have specific protective effects against oncogenesis as well as tumor growth and response to treatment.

10. Conclusion

Obesity contributes to increased risk for multiple solid cancers including pancreatic cancer. For pancreatic cancer in particular, obesity promotes a proinflammatory environment which promotes oncogenesis, tumor growth, metastatic spread as well as resistance to therapy through a variety of molecular pathways. The principle obesity-linked pathways include increases in TNF-α, IL-1, IL-6, IL-8, IL-10 and IL-23 as well as activation of NF-κB and STAT3. The current diets of industrialized nations which contain too much low glycemic-index carbohydrates, saturated fats, and HFCS are major environmental triggers of pathologic TLR3 and TLR4 signaling pathways in adipocytes which then contribute to the development of insulin resistance, ectopic fat deposition in multiple tissues including the pancreas which in turn amplify the growth and signaling pathways described herein which lead to oncogenesis and tumor spread.

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