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Smoking and Pancreatic Disease

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Abstract

Smoking is a major risk factor for chronic pancreatitis and pancreatic cancer. However, the mechanisms through which it causes the diseases remain unknown. In the present manuscript we reviewed the latest knowledge gained on the effect of cigarette smoke and smoking compounds on cell signaling pathways mediating both diseases. We also reviewed the effect of smoking on the pancreatic cell microenvironment including inflammatory cells and stellate cells.

Keywords

Smoking; Pancreatitis; Pancreatic Cancer

1. Introduction

Numerous studies have shown that cigarette smoking increases the risk of developing pancreatic cancer, although its contribution to pancreatitis has only been appreciated in recent years [1-3]. Clinical advances have identified a role for cigarette smoke in pancreatitis, but experimental data regarding its disease mechanism are scarce. In this review, advances in basic science research are summarized, regarding the role of cigarette smoke, and it's most potent constituents, in pancreatitis and pancreatic cancer.

Factors Involved in Smoking-Related Pancreatic Disease

Of the 4000 chemicals in cigarette smoke, greater than 60 have been identified as prospective carcinogens. Tobacco smoke and its various components, including nicotine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), and other tobacco specific nitrosamines have been studied in cells and *in vivo* [4-11]. In laboratory animals, the most potent nicotine metabolite is NNK [12]. Other nitrosamines formed from nicotine include N'-nitrosonor-nicotine (NNN) and Diethylnitrosamine [13]. These nicotine metabolites are potentially formed via nitrosation during processing of the tobacco plant [14]. It has been reported that roughly 46% of NNN and 26% - 37% of NNK in tobacco are preformed and the remainder is pyrosynthesized from nicotine during smoking [15]. Of these constituents, nicotine and NNK are the most studied constituents with respect to pancreatic disease. Other potentially harmful components of tobacco smoke include polycyclic aromatic hydrocarbons, although their role in pancreatic disease is undetermined [15,16].

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Few reliable animal models of smoking and pancreatic disease have been developed, and little is known about underlying cellular mechanisms. Those that have been established involve exposure of rodents to cigarette smoke in specialized smoke-delivery chambers, or ingestion/injection of a tobacco toxin over a period of time. The subsequent sections will focus on some of these models and underscore the latest developments in our understanding of smoking-related pancreatitis and pancreatic cancer.

2. Smoking and Pancreatitis

2.1. Cigarette Smoke Exposure and Pancreatitis

In models of cigarette smoke exposure over a period of weeks rats developed pancreatic damage, elevated pancreatic levels of the digestive zymogens, trypsinogen and chymotrypsinogen, [5] and altered gene expression, affecting the ratio of trypsinogen to its endogenous inhibitor (pancreas-specific trypsin inhibitor; PSTI). Smoke-exposed animals had increased susceptibility to pancreatitis as a result of these changes [7]. Given that smoking exacerbates the clinical effects of alcohol in pancreatitis, one model combined smoke treatment with ethanol consumption; pancreatic ischemia worsened and increased leukocyte infiltration was seen [9].

While these studies are informative, they only describe effects of smoke; they do not identify relevant toxins or how they initiate these cellular effects. The studies detailed in subsequent sections focus on nicotine and its potent metabolite NNK, revealing a role for these nitrosamines and potential pathways underlying disease initiation.

2.2. Nicotine and NNK-Mediated Pathways in Pancreatitis

Nicotine is a key toxin in tobacco and cigarettes and may contribute to the development of pancreatitis and pancreatic cancer. Nicotine is swiftly absorbed in the lungs and is eliminated from the body within 120 - 180 minutes [17]. Metabolism of nicotine primarily occurs via the cytochrome P450 (CYP) 2A6 pathway along with other enzymes including aldehyde oxidase 1, UDP-glucuronosyltranferases, flavin-containing monooxygenase 3 and other CYPs e.g. 2A13, 2B6. Polymorphisms in CYP2A6 have been related to racial and genetic variations in nicotine metabolism, but it is unknown if these contribute to smoking-related pancreatic disease [18]. Moreover, elevated P450 enzyme levels have been reported in patients with chronic pancreatitis and pancreatic cancer as compared to healthy controls [19]. Rats exposed to ^{3}H-nicotine saw a noticeable buildup of it in the pancreas and intestine [19,20]. Further, metabolites of nicotine were detected in samples of human pancreatic juice from smokers. Cotinine, the primary nicotine metabolite, was present at levels of 129 +/− 156 ng/ml followed by NNK at 1.37 ng/ml to 600 ng/ml (0.7μM and 6.6 nM - 3 μM respectively) [21]. These levels of nicotine metabolites may be sufficient to activate cell surface receptors on the exocrine pancreas that could mediate pancreatitis and pancreatic cancer responses.

Studies have been undertaken to ascertain the pathological and functional effects of nicotine on the pancreas. In several studies, nicotine exposure resulted in cytoplasmic swelling, vacuolization, pyknotic nuclei and karyorrhexis, which were localized to the exocrine pancreas. Furthermore, a decreased secretory response was observed. along with increased retention of pancreatic pro-enzymes [4,22-29]. A recent study has shown that secretory effects induced by nicotine in isolated rat acini were abrogated following treatment with a nicotinic receptor antagonist and calcium channel antagonists [28]. These findings indicate that nicotine effects are mediated via a nicotinic acetylcholine receptor (nAChR) and calcium is the resultant signaling pathway. Nicotine also has been shown to alter basal levels of GI hormones (gastrin; CCK) and serum enzymes such as amylase and lipase in blood circulation in rats [24]. Such changes have been linked to morphological changes observed

during pancreatitis [19,27]. Nicotine has also been shown to modulate oxidative stress and lipid peroxidation although it is unclear if these processes participate in the pathophysiology of acute and chronic pancreatitis [29].

The nicotine metabolite, NNK, is one of the most abundant and injurious tobacco-specific carcinogens. It is a high-affinity agonist of nicotinic acetylcholine receptors (nAChR) and may affect the development of pancreatic cancer through receptor-mediated pathways [10,13]. These receptors were first characterized within the nervous system, but have since been shown to be present in non-neuronal cells [13]. Cancer cell lines as well as human keratinocytes and epithelial cells has been shown to have α7 nAChR and respond to NNK (EC50 for NNK = 0.03 μM). Although nicotine is 5000 - 10000 times more concentrated in tobacco smoke than NNK and 2000 - 3000 times more concentrated than NNN, NNK shows 1000-fold higher affinity for α7 nAChR compared to nicotine. Additionally, α7 nAchRs are up-regulated in the organs of smokers, and experimentally in the pancreas and lungs of rodents following chronic nicotine/NNK exposure [8,13].

The role of NNK as an initiator of acute pancreatitis in rats was described recently by Alexandre *et al.*, [30]. Using isolated acinar cells and in vivo models of pancreatitis, they demonstrated that NNK induced premature activation of digestive zymogens (trypsinogen and chymotrypsinogen), a pivotal event in initiating pancreatitis. Cerulein (an orthologue of the hormone cholecystokinin; CCK) is commonly used in isolated pancreatic acinar cells or animals in supraphysiologic concentrations (10 - 100 x that required to induce physiological responses), to cause experimental pancreatitis. NNK treatment in a cerulein model of the disease elevated zymogen activation above that seen with NNK or cerulein treatment alone. Furthermore, NNK triggered cellular damage in the pancreas (vacuolization, pyknotic nuclei, and edema) consistent with that observed during acute pancreatitis. The NNK receptor target, α-7 nAChR, was detected in rat acini by PCR analysis. In addition, NNK mediated zymogen activation was completely abrogated when isolated acini were pre-treated with mecamylamine (a nAChR blocker), validating a key role for α-7 nAChR in triggering smoking-related pancreatitis. These findings are the first to identify direct effects of cigarette toxins on the acinar cell through a receptor-mediated mechanism.

NNK may also stimulate pancreatitis responses via β-adrenergic receptors. NNK is structurally similar to classic β-adrenergic agonists and has high affinity for human β-1 and β-2 receptors, with a preference for β-1 (EC_{50} for β1 = 5.8 nM; EC_{50} for β2 = 128 nM) [31]. Activation of β-adrenergic receptors results in activation of adenylate cyclase, generation of cAMP, or release of arachidonic acid. Elevations in cAMP have been implicated in pancreatitis responses [32]. The enzyme phospholipase A2 (PLA2) mediates arachidonic acid release which is an important facilitator of inflammation; iso-forms of phospholipase A2-II and A2-IV are elevated during human acute pancreatitis and may contribute to inflammatory effects through this pathway [33]. One study identified β-1 and β-2 adrenergic receptors in rat acini by PCR analysis, however the β-adrenergic receptor blocker propranolol did not prevent NNK-mediated zymogen activation in isolated acini [30].

Whether NNK potentiates additional pancreatitis responses through nicotinic, β-adrenergic, or other receptors remains a focus for future research.

2.3. Regulation of Inflammation by Smoke Compounds in Pancreatitis

NNK and nicotine may exert influence over inflammatory cells during pancreatitis by binding to α7 nAChR expressed on macrophages, thereby modulating immune responses. Nicotine blocks production of pro-inflammatory cytokines from macrophages by inhibiting the NFκB pathway, which is involved in macrophage activation [24,35]. Furthermore, treatment of mice with mecamylamine (α7 nAChR blocker) decreased neutrophil and

macrophage migration to pancreatic tissue and intensified severity of experimental pancreatitis [36]. Prolonged exposure to cigarette smoke, however, results in chronic inflammation in the pancreas, indicating that an anti-inflammatory effect may be a short term response that gives way to a chronic inflammatory phase [37]. Pro-inflammatory effects of NNK may be a result of its up-take and metabolism by macrophages. In U937 human macrophages NNK was metabolized and subsequently it activated NFκB, causing TNFα release which promotes inflammation [10]. Therefore, NNK and other tobacco derived nitrosamines likely mediate early pancreatitis events through interaction with α7 nAChR on acini and macrophages; chronic-inflammatory responses occur much later, perhaps through uptake and metabolism of such compounds.

3. Smoking and Pancreatic Cancer

Tobacco smoking is a major established risk factor for pancreatic cancer [21,38]. It increases the risk of pancreatic cancer up to 6-fold depending on the duration and intensity of smoking [39-41]. Nearly one quarter of all pancreatic cancer deaths are linked to tobacco use [42]. Two different studies published recently showed that smokers are diagnosed with pancreatic cancer at ages 8 to 15 years younger than non-smokers [43,44]. Therefore, understanding the mechanisms through which smoking predisposes to pancreatic cancer is urgently needed. This will help target patients at high risk for the disease with preventive strategies, and permit development of treatment approaches directed at cell signaling pathways involved in smoking-induced pancreatic cancer.

3.1. Cigarette Smoke-Mediated Pathways in Pancreatic Cancer

As in chronic pancreatitis, slight progress has been achieved in understanding the signaling pathways regulated by cigarette smoke compounds in pancreatic cancer in recent years.

A major mechanism through which smoking compounds predispose to cancer in general is through inducing DNA adducts leading to genetic mutations. However, analysis of the pancreatic tissue did not show any association between increased level of mutations of pancreatic cancer-associated genes such as K-ras and p53 and smoking [45,46]. However, the same study found association between increases in less common mutations in pancreatic cancer patients and smoking status suggesting possible role of these mutations in mediating the smoking pro-cancer effect in the pancreas [46].

As discussed earlier, major cigarette smoke carcinogen NNK interacts with pancreatic cells through β-adrenergic receptor and nAChR [6,47-49]. These receptors mediate NNK activation of Cox2, EGFR and Erk in pancreatic cancer cells and ductal cells [47,48]. These pathways regulate proliferation and cell death in pancreatic cells.

We showed that NNK and cigarette smoke extract stimulate proliferation and inhibit apoptosis of normal pancreatic ductal cells through a mechanism that involves Akt and AMP kinases [50]. In pancreatic cancer cells nicotine stimulates proliferation and invasion of the AsPC1 pancreatic cancer cell line. Furthermore, nicotine stimulates epithelial to mesenchymal transition (EMT) by down-regulating E-cadherin and β-catenin and up-regulating vimentin and fibronectin in several cancer cells [51]. EMT has been associated with acquiring cancer stem cells characteristics suggesting regulation of pancreatic cancer stemness and resistance to treatment by smoking compounds.

In fact, recent data indicate that nicotine stimulates growth, invasion, and resistance of pancreatic cancer cells to chemotherapy through a mechanism that involves Src pathways and the inhibitor of differentiation-1 (Id1) transcription factor [52]. These effects were mediated by the α7 nAChR receptor.

Regulation of EMT/invasion/metastasis pathways and resistance to chemotherapeutic agents is extremely important to understand as these are the major contributors to the aggressiveness of pancreatic cancer. The data published in the last few years suggest that smoking compounds do not only contribute to the initiation of cancer, but also to the progression and the transformation of the cancer cells making them more metastatic and resistant to drugs. EMT and stemness pathways regulated by smoking compounds need to be further investigated.

3.2. Cigarette Smoke and Regulation of the Microenvironment of the Pancreatic Tumors

Pancreatic cancer is characterized by a strong desmo-plastic reaction that includes inflammatory cells infiltration and fibrosis. There is increasing awareness of the role of the tumor microenvironment in progression of the disease.

Smoking compounds can worsen chronic pancreatitis leading to pancreatic cancer [53]. Fibrosis and inflammation are major characteristics of chronic pancreatitis. Exposure to cigarette smoke stimulates both fibrosis and inflammation in the pancreas of rats [54].

Extracellular matrix proteins (ECM) secretion leading to fibrosis is mainly mediated by activated pancreatic stellate cells. These cells have been shown to express nicotinic acetylcholine receptors and respond to nicotine exposure by increased proliferation and ECM production [55]. ECM production contributes to pancreatic cancer cell survival and resistance to apoptosis [56].

Differently from the effect of smoking on inflammation in chronic pancreatitis [30,33], very little is known about how inflammatory response would mediate smoking-induced pancreatic cancer.

NNK treatment has been shown to significantly increase macrophage infiltration and expression of pro-inflammatory mediators such as macrophage inflammatory protein 1 alpha (MIP-1α), interleukin 1 beta (IL-1β), and transforming growth factor-beta (TGF-β) in mice neoplastic lesions [5]. Macrophage and mast cell infiltration is observed in human pancreatic cancer as well [57].

Recent data showed that cigarette smoke extract significantly stimulated pancreatic ductal epithelial flattening and induced severe acini atrophy in Elastase-IL-1β transgenic mice. Cigarette smoke extract stimulated proliferation and inhibited apoptosis in pancreatic ductal epithelial cells in this model. Furthermore, analysis of the cell signaling pathways showed induction of COX-2 in the setting of chronic inflammation. A very recent paper showed that high fat diet activates oncogenic Kras via COX2 leading to pancreatic inflammation and fibrosis, and development of pancreatic intraepithelial neoplasia lesions and pancreatic ductal adenocarcinoma [58].

3.3. Future Directions

The lack of good animal models to study pancreatic cancer contributed to the slow progress in understanding how smoking causes the disease. Previous studies using hamsters and rats showed pro-cancer effect of the smoking compounds but only after very long time (1 to 2 years) [12,59]. More recent animal models combining cigarette smoke compounds with carcinogenic chemicals such as 7,12-dimethylbenzanthracene (DMBA) or using orthotopic model of pancreatic cancer showed faster progression of the disease [59,60]. Developing mouse models of pancreatic cancer based on K-ras mice is greatly required and will serve as a useful tool in understanding the disease. These models will provide a good base to study the interaction between immune cells, stellate cells and pancreatic cancer cells in early and late stage of the disease.

4. Conclusion

The last few years have seen slow progress in understanding the effect of cigarette smoking on pancreatic disease. Smoking is a risk factor for acute and chronic pancreatitis, and pancreatic cancer. It also increases the risk of pancreatic cancer in patients with pancreatitis. Identification of cellular targets, such as nAChR, will help in development of potential therapies. Furthermore, the use of reliable animal models such as the Pdx1-Cre, LSL-Kras mice will help dissect relevant cellular changes in the pancreas induced by smoking.

REFERENCES

[1]. Tolstrup JS, Kristiansen L, Becker U, et al. Smoking and Risk of Acute and Chronic Pancreatitis among Women and Men: A Population-Based Cohort Study. Archives of Internal Medicine. 2009; Vol. 169(No. 6):603–609. http://dx.doi.org/10.1001/archinternmed.2008.601.

[2]. Yadav D, Hawes RH, Brand RE, et al. Alcohol Consumption, Cigarette Smoking, and the Risk of Recurrent Acute and Chronic Pancreatitis. Archives of Internal Medicine. 2009; Vol. 169(No. 11):1035–1045. http://dx.doi.org/10.1001/archinternmed.2009.125. [PubMed: 19506173]

[3]. Sadr-Azodi O, Andren-Sandberg A, Orsini N, Wolk A. Cigarette Smoking, Smoking Cessation and Acute Pancreatitis: A Prospective Population-Based Study. Gut. 2012; Vol. 61(No. 2):262–267. [PubMed: 21836026]

[4]. Chowdhury P. An Exploratory Study on the Development of an Animal Model of Acute Pancreatitis Following Nicotine Exposure. Tobacco Induced Diseases. 2003; Vol. 1:213–217. http://dx.doi.org/10.1186/1617-9625-1-3-213. [PubMed: 19570262]

[5]. Wittel UA, Pandey KK, Andrianifahanana M, et al. Chronic Pancreatic Inflammation Induced by Environmental Tobacco Smoke Inhalation in Rats. The American Journal of Gastroenterology. 2006; Vol. 101(No. 1):148–159. http://dx.doi.org/10.1111/j.1572-0241.2006.00405.x. [PubMed: 16405548]

[6]. Askari MD, Tsao MS, Cekanova M, et al. Ethanol and the Tobacco-Specific Carcinogen, NNK, Contribute to Signaling in Immortalized Human Pancreatic Duct Epithelial Cells. Pancreas. 2006; Vol. 33(No. 1):53–62. http://dx.doi.org/10.1097/01.mpa.0000226883.55828.e9.

[7]. Wittel UA, Singh AP, Henley BJ, et al. Cigarette Smoke-Induced Differential Expression of the Genes Involved in Exocrine Function of the Rat Pancreas. Pancreas. 2006; Vol. 33:364–370. http://dx.doi.org/10.1097/01.mpa.0000240601.80570.31. [PubMed: 17079941]

[8]. Al-Wadei HA, Schuller HM. Nicotinic Receptor-Associated Modulation of Stimulatory and Inhibitory Neurotransmitters in NNK-Induced Adenocarcinoma of the Lungs and Pancreas. The Journal of Pathology. 2009; Vol. 218(No. 4):437–445. http://dx.doi.org/10.1002/path.2542. [PubMed: 19274673]

[9]. Hartwig W, Werner J, Ryschich E, et al. Cigarette Smoke Enhances Ethanol-Induced Pancreatic Injury. Pancreas. 2000; Vol. 21(No. 3):272–278. http://dx.doi.org/10.1097/00006676-200010000-00009. [PubMed: 11039472]

[10]. Rioux N, Castonguay A. 4-(Methylnitrosamino)-1-(3-Pyridyl)-1-Butanone Modulation of Cytokine Release in U937 Human Macrophages. Cancer Immunology, Immunotherapy. 2001; Vol. 49:663–670. http://dx.doi.org/10.1007/s002620000157.

[11]. Trushin N, Leder G, El-Bayoumy K, et al. The Tobacco Carcinogen NNK is Stereoselectively Reduced by Human Pancreatic Microsomes and Cytosols. Langen-beck's Archives of Surgery. 2008; Vol. 393(No. 4):571–579. http://dx.doi.org/10.1007/s00423-007-0265-3.

[12]. Rivenson A, Hoffmann D, Prokopczyk B, et al. Induction of Lung and Exocrine Pancreas Tumors in F344 Rats by Tobacco-Specific and Areca-Derived N-Ni-trosamines. Cancer Research. 1988; Vol. 48(No. 23):6912–6917. [PubMed: 3180100]

[13]. Schuller HM. Nitrosamines as Nicotinic Receptor Ligands. Life Sciences. 2007; Vol. 80(No. 24-25):2274–2280. http://dx.doi.org/10.1016/j.lfs.2007.03.006. [PubMed: 17459420]

[14]. Hecht SS. Biochemistry, Biology, and Carcinogenicity of Tobacco-Specific N-Nitrosamines. Chemical Research in Toxicology. 1998; Vol. 11(No. 6):559–603. http://dx.doi.org/10.1021/tx980005y. [PubMed: 9625726]

[15]. Ding YS, Zhang L, Jain RB, et al. Levels of Tobacco-Specific Nitrosamines and Polycyclic Aromatic hydrocarbons in Mainstream Smoke from Different Tobacco Varieties. Cancer Epidemiology, Biomarkers & Prevention. 2008; Vol. 17:3366–3371. http://dx.doi.org/10.1158/1055-9965.EPI-08-0320.

[16]. Anderson KE, Hammons GJ, Kadlubar FF, et al. Metabolic Activation of Aromatic Amines by Human Pancreas. Carcinogenesis. 1997; Vol. 18(No.):1085–1092. http://dx.doi.org/10.1093/carcin/18.5.1085. [PubMed: 9163700]

[17]. Chowdhury P, Rayford PL. Smoking and Pancreatic Disorders. European Journal of Gastroenterology & Hepatology. 2000; Vol. 12:869–877. http://dx.doi.org/10.1097/00042737-200012080-00006. [PubMed: 10958214]

[18]. Mwenifumbo JC, Tyndale RF. Molecular Genetics of Nicotine Metabolism. Handbook of Experimental Pharmacology. 2009; Vol. 192:235–259. [PubMed: 19184652]

[19]. Chowdhury P, MacLeod S, Udupa KB, et al. Pathophysiological Effects of Nicotine on the Pancreas: An Update. Experimental Biology and Medicine. 2002; Vol. 227(No. 7):445–454. [PubMed: 12094008]

[20]. Chowdhury P, Doi R, Chang LW, et al. Tissue Distribution of [3H]-Nicotine in Rats. Biomedical and Environmental Sciences. 1993; Vol. 6(No. 1):59–64. [PubMed: 8476533]

[21]. Prokopczyk B, Hoffmann D, Bologna M, et al. Identification of Tobacco-Derived Compounds in Human Pancreatic Juice. Chemical Research in Toxicology. 2002; Vol. 15(No. 5):677–685. http://dx.doi.org/10.1021/tx0101088. [PubMed: 12018989]

[22]. Chowdhury P, Hosotani R, Chang L, et al. Metabolic and Pathologic Effects of Nicotine on Gastrointestinal Tract and Pancreas of Rats. Pancreas. 1990; Vol. 5:222–229. http://dx.doi.org/10.1097/00006676-199003000-00016. [PubMed: 1690423]

[23]. Chowdhury P, Rayford PL, Chang LW. Induction of Pancreatic Acinar Pathology via Inhalation of Nicotine. Proceedings of the Society for Experimental Biology and Medicine. 1992; Vol. 201(No. 2):159–164. http://dx.doi.org/10.3181/00379727-201-43494B. [PubMed: 1409731]

[24]. Chowdhury P, Hosotani R, Rayford PL. Inhibition of CCK or Carbachol-Stimulated Amylase Release by Nicotine. Life Sciences. 1989; Vol. 45(No. 22):2163–2168. http://dx.doi.org/10.1016/0024-3205(89)90083-0. [PubMed: 2481202]

[25]. Chowdhury P, Rayford PL, Chang LW. Pathophysiological Effects of Nicotine on the Pancreas. Proceedings of the Society for Experimental Biology and Medicine. 1998; Vol. 218(No. 3):168–173. http://dx.doi.org/10.3181/00379727-218-44284. [PubMed: 9648934]

[26]. Lindkvist B, Wierup N, Sundler F, et al. Long-Term Nicotine Exposure Causes Increased Concentrations of Trypsinogens and Amylase in Pancreatic Extracts in the Rat. Pancreas. 2008; Vol. 37:288–294. http://dx.doi.org/10.1097/MPA.0b013e31816a7744. [PubMed: 18815551]

[27]. Chowdhury P, Bose C, Udupa KB. Nicotine-Induced Proliferation of Isolated Rat Pancreatic Acinar Cells: Effect on Cell Signalling and Function. Cell Proliferation. 2007; Vol. 40(No. 1):125–141. http://dx.doi.org/10.1111/j.1365-2184.2007.00418.x. [PubMed: 17227300]

[28]. Chowdhury P, Udupa KB. Effect of Nicotine on Exocytotic Pancreatic Secretory Response: Role of Calcium Signaling. Tobacco Induced Diseases. 2013; Vol. 11(No. 1):1. http://dx.doi.org/10.1186/1617-9625-11-1. [PubMed: 23327436]

[29]. Chowdhury P, Walker A. A Cell-Based Approach to Study Changes in the Pancreas Following Nicotine Exposure in an Animal Model of Injury. Langenbeck's Archives of Surgery. 2008; Vol. 393(No. 4):547–555. http://dx.doi.org/10.1007/s00423-007-0267-1.

[30]. Alexandre M, Uduman AK, Minervini S, Raoof A, Shugrue CA, Akinbiyi EO, Patel V, Shitia M, Kolodecik TR, Patton R, Gorelick FS, Thrower EC. Tobacco Carcinogen 4-(Methylnitrosamino)-1-(3-Pyridyl)-1-Butanone Initiates and Enhances Pancreatitis Responses. The American Journal of Physiology—Gastrointestinal and Liver Physiology. 2012; Vol. 303:G696–704. http://dx.doi.org/10.1152/ajpgi.00138.2012.

[31]. Schuller HM, Tithof PK, Williams M, et al. The Tobacco-Specific Carcinogen 4-(Methylnitrosamino)-1-(3-Pyridyl)-1-Butanone is a Beta-Adrenergic Agonist and Stimulates DNA Synthesis in Lung Adenocarcinoma via Beta-Adrenergic Receptor-Mediated Release of Arachidonic Acid. Cancer Research. 1999; Vol. 59(No. 18):4510–4515. [PubMed: 10493497]

[32]. Chaudhuri A, Kolodecik TR, Gorelick FS. Effects of Increased Intracellular cAMP on Carbachol-stimulated Zymogen Activation, Secretion, and Injury in the Pancreatic Acinar Cell. The American Journal of Physiology—Gastrointestinal and Liver Physiology. 2005; Vol. 288:G235–243. http://dx.doi.org/10.1152/ajpgi.00334.2004.

[33]. Friess H, Shrikhande S, Riesle E, et al. Phospholipase A2 Isoforms in Acute Pancreatitis. Annals of Surgery. 2001; Vol. 233(No. 2):204–212. http://dx.doi.org/10.1097/00000658-200102000-00009. [PubMed: 11176126]

[34]. Ulloa L. The Vagus Nerve and the Nicotinic Anti-Inflammatory Pathway. Nature Reviews Drug Discovery. 2005; Vol. 4(No. 8):673–684. http://dx.doi.org/10.1038/nrd1797.

[35]. Wang H, Yu M, Ochani M, et al. Nicotinic Acetylcholine Receptor Alpha7 Subunit is an Essential Regulator of Inflammation. Nature. 2003; Vol. 421(No. 6921):384–388. http://dx.doi.org/10.1038/nature01339. [PubMed: 12508119]

[36]. Westerloo, D. J. Van; Giebelen, IA.; Florquin, S.; Bruno, MJ.; Larosa, GJ.; Ulloa, L.; Tracey, KJ.; van der Poll, T. The Vagus Nerve and Nicotinic Receptors Modulate Experimental Pancreatitis Severity in Mice. Gastroentero-logy. 2006; Vol. 130(No. 6):1822–1830. http://dx.doi.org/10.1053/j.gastro.2006.02.022.

[37]. Greer JB, Whitcomb DC. Inflammation and Pancreatic Cancer: An Evidence Based Review. Current Opinion in Pharmacology. 2009; Vol. 9(No. 4):411–418. http://dx.doi.org/10.1016/j.coph.2009.06.011.

[38]. Lowenfels AB, Maisonneuve P. Environmental Factors and Risk of Pancreatic Cancer. Pancreatology. 2003; Vol. 3(No. 1):1–8. http://dx.doi.org/10.1159/000069140. [PubMed: 12683400]

[39]. Raimondi S, Maisonneuve P, Löhr JM, Lowenfels AB. Early Onset Pancreatic Cancer: Evidence of a Major Role for Smoking and Genetic Factors. Cancer Epidemiology Biomarks & Prevention. 2007; Vol. 16(No. 9):1894–1897.

[40]. Whittemore AS, Paffenbarger RS Jr. Anderson K, Halpern J. Early Precursors of Pancreatic Cancer in College Men. Journal of Chronic Diseases. 1983; Vol. 36(No. 3):251–256. http://dx.doi.org/10.1016/0021-9681(83)90059-0. [PubMed: 6826689]

[41]. Iodice S, Gandini S, Maisonneuve P, Lowenfels AB. Tobacco and the Risk of Pancreatic Cancer: A Review and Meta-Analysis. Langenbeck's Archives of Surgery. 2008; Vol. 393(No. 4):535–545. http://dx.doi.org/10.1007/s00423-007-0266-2.

[42]. Mack TM, Yu MC, Hanisch R, Henderson BE. Pancreas Cancer and Smoking, Beverage Consumption, and Past Medical History. Journal of National Cancer Institute. 1986; Vol. 76(No. 1):49–60.

[43]. Maisonneuve P, Lowenfels AB. Epidemiology of Pancreatic Cancer: An Update. Digestive Disease. 2010; Vol. 28(No. 4-5):645–656. http://dx.doi.org/10.1159/000320068.

[44]. Anderson MA, Zolotarevsky E, Cooper KL, Sherman S, Shats O, Whitcomb DC, Lynch HT, Ghiorzo P, Rubinstein WS, Vogel KJ, Sasson AR, Grizzle WE, Ketcham MA, Lee SY, Normolle D, Plonka CM, Mertens AN, Tripon RC, Brand RE. Alcohol and Tobacco Lower the Age of Presentation in Sporadic Pancreatic Cancer in a Dose-Dependent Manner: A Multicenter Study. American Journal of Gastroenterology. 2012; Vol. 107(No. 11):1730–1739. http://dx.doi.org/10.1038/ajg.2012.288. [PubMed: 22929760]

[45]. Porta M, Crous-Bou M, Wark PA, Vineis P, Real FX, Malats N, Kampman E. Cigarette Smoking and K-Ras Mutations in Pancreas, Lung and Colorectal Adenocarcinomas: Etiopathogenic Similarities, Differences and Paradoxes. Mutation Research. 2009; Vol. 682(No. 2-3):83–93. http://dx.doi.org/10.1016/j.mrrev.2009.07.003. [PubMed: 19651236]

[46]. Blackford A, Parmigiani G, Kensler TW, et al. Genetic Mutations Associated with Cigarette Smoking in Pancreatic Cancer. Cancer Research. 2009; Vol. 69(No. 8):3681–3688. http://dx.doi.org/10.1158/0008-5472.CAN-09-0015. [PubMed: 19351817]

[47]. Weddle DL, Tithoff P, Williams M, Schuller HM. Beta-Adrenergic Growth Regulation of Human Cancer Cell Lines Derived from Pancreatic Ductal Carcinomas. Carcinogenesis. 2001; Vol. 22(No. 3):473–479. http://dx.doi.org/10.1093/carcin/22.3.473. [PubMed: 11238189]

[48]. Askari MD, Tsao MS, Schuller HM. The Tobacco-Specific Carcinogen, 4-(methylnitrosamino)-1-(3-pyridyl)-1-Butanone Stimulates Proliferation of Immortalized Human

Pancreatic Duct Epithelia through Beta-Adrenergic Transactivation of EGF Receptors. Journal of Cancer Research and Clinical Oncology. 2005; Vol. 131(No. 10):639–648. http://dx.doi.org/10.1007/s00432-005-0002-7. [PubMed: 16091975]

[49]. Yoshikawa H, Hellström-Lindahl E, Grill V. Evidence for Functional Nicotinic Receptors on Pancreatic Beta Cells. Metabolism. 2005; Vol. 54(No. 2):247–254. http://dx.doi.org/10.1016/j.metabol.2004.08.020. [PubMed: 15690320]

[50]. Park CH, Lee IS, Grippo P, Pandol SJ, Gukovskaya AS, Edderkaoui M. Akt Kinase Mediates the Prosurvival Effect of Smoking Compounds in Pancreatic Ductal Cells. Pancreas. 2013; Vol. 42(No. 4):655–662. http://dx.doi.org/10.1097/MPA.0b013e3182762928. [PubMed: 23271397]

[51]. Dasgupta P, Rizwani W, Pillai S, Kinkade R, Kovacs M, Rastogi S, Banerjee S, Carless M, Kim E, Coppola D, Haura E, Chellappan S. Nicotine Induces Cell Proliferation, Invasion and Epithelial-Mesenchymal Transition in a Variety of Human Cancer Cell Lines. International Journal of Cancer. 2009; Vol. 124(No. 1):36–45. http://dx.doi.org/10.1002/ijc.23894.

[52]. Trevino JG, Pillai S, Kunigal S, Singh S, Fulp WJ, Centeno BA, Chellappan SP. Nicotine Induces Inhibitor of Differentiation-1 in a Src-Dependent Pathway Promoting Metastasis and Chemoresistance in Pancreatic Adenocarcinoma. Neoplasia. 2012; Vol. 14(No. 12):1102–1114. [PubMed: 23308043]

[53]. Alexandre M, Pandol SJ, Gorelick FS, Thrower EC. The Emerging Role of Smoking in the Development of Pancreatitis. Pancreatology. 2011; Vol. 11(No. 5):469–474. http://dx.doi.org/10.1159/000332196. [PubMed: 21986098]

[54]. Dubick MA, Palmer R, Lau PP, Morrill PR, Geokas MC. Altered Exocrine Pancreatic Function in Rats Treated with Nicotine. Toxicology and Applied Pharmacology. 1988; Vol. 96(No. 1):132–139. http://dx.doi.org/10.1016/0041-008X(88)90255-4. [PubMed: 2460970]

[55]. Lau PP, Dubick MA, Yu GS, Morrill PR, Geokas MC. Dynamic Changes of Pancreatic Structure and Function in Rats Treated Chronically with Nicotine. Toxicology and Applied Pharmacology. 1990; Vol. 104(No. 3):457–465. http://dx.doi.org/10.1016/0041-008X(90)90167-S.

[56]. Edderkaoui M, Hong P, Vaquero EC, Lee JK, Fischer L, Friess H, Buchler MW, Lerch MM, Pandol SJ, Gukovskaya AS. Extracellular Matrix Stimulates Reactive Oxygen Species Production and Increases Pancreatic Cancer Cell Survival through 5-Lipoxygenase and NADPH Oxidase. American Journal of Physiology. Gastrointestinal and Liver Physiology. 2005; Vol. 289(No. 6):G1137–G1147. http://dx.doi.org/10.1152/ajpgi.00197.2005.

[57]. Esposito I, Menicagli M, Funel N, Bergmann F, Boggi U, Mosca F, Bevilacqua G, Campani D. Inflammatory Cells Contribute to the Generation of an Angiogenic Phenotype in Pancreatic Ductal Adenocarcinoma. Journal of Clinical Pathology. 2004; Vol. 57(No. 6):630–636. http://dx.doi.org/10.1136/jcp.2003.014498. [PubMed: 15166270]

[58]. Philip B, Roland CL, Daniluk J, Liu Y, Chatterjee D, Gomez SB, Ji B, Huang HJ, Wang HM, Fleming JB, Logsdon CD, Cruz-Monserrate Z. A High-Fat Diet Activates Oncogenic Kras and COX2 to Induce Development of Pancreatic Ductal Adenocarcinoma in Mice. Gastroenterology. 2013 (in press).

[59]. Momi N, Ponnusamy MP, Kaur S, Rachagani S, Kunigal SS, Chellappan S, Ouellette MM, Batra SK. Nicotine/Cigarette Smoke Promotes Metastasis of Pancreatic Cancer through α7nAChR-mediated MUC4 Upregulation. Oncogene. 2013; Vol. 32(No. 11):1384–1395. http://dx.doi.org/10.1038/onc.2012.163. [PubMed: 22614008]

[60]. Nicolov IG, Chernozemsky IN. Tumors and hyperplastic lesions in Syrian Hamsters Following Trans-placental and Neonatal Treatment with Cigarette Smoke Condensate. Journal of Cancer Research and Clinical Oncology. 1979; Vol. 94(No. 3):249–256. [PubMed: 479264]