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Review

The Role of Gastrin and CCK Receptors in Pancreatic Cancer and other Malignancies

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Abstract

The gastrointestinal (GI) peptide gastrin is an important regulator of the release of gastric acid from the stomach parietal cells and it also plays an important role in growth of the gastrointestinal tract. It has become apparent that gastrin and its related peptide cholecystokinin (CCK) are also significantly involved with growth of GI cancers as well as other malignancies through activation of the cholecystokinin-B (CCK-B) receptor. Of interest, gastrin is expressed in the embryologic pancreas but not in the adult pancreas; however, gastrin becomes re-expressed in pancreatic cancer where it stimulates growth of this malignancy by an autocrine mechanism. Strategies to down-regulate gastrin or interfere with its interface with the CCK receptor with selective antibodies or receptor antagonists hold promise for the treatment of pancreatic cancer and other gastrin – responsive tumors.

Key words: peptide gastrin

Introduction

Advanced pancreatic cancer has a dismal prognosis [1, 2] and the current chemotherapeutic regimens have not significantly improved survival [3]. With the current rise in incidence of pancreatic cancer it is anticipated that this malignancy will surpass colon and breast cancer in the next decade to become the second leading cause of cancer-related deaths in the USA [4]. In this new era of precision medicine, genomic profiling and target-specific therapies to cancer specific receptors has improved the outcome of many recalcitrant cancers [5, 6]. Immune-based therapies have also led to improvements in cancer survival in the past decade [7], especially for the treatment of advanced melanoma [8]. One reason the survival and response to therapies has been so poor for pancreatic cancer is because the current chemotherapeutic regimens are not target specific.

Similar to other malignancies, pancreatic cancer possesses unique growth-related receptors that when activated stimulate tumor proliferation. One such receptor that has been identified and characterized on pancreatic cancer is the cholecystokinin (CCK) receptor, and this receptor is markedly over-expressed in pancreatic cancer [9, 10]. Activation of the CCK receptor in pancreatic cancer by its ligands gastrin [11] or CCK [12, 13] induces signaling through the AKT pathway [14] resulting in cell proliferation. Gastrin is expressed in the developing fetal pancreas where it is thought to play an important role in pancreatic growth and differentiation [15]; however, gastrin expression is turned off at week 14 in the embryo and becomes re-expressed in precancerous lesions of the pancreas, i.e., pancreatic intraepithelial neoplasias (PanINs) [16]. Furthermore, gastrin is markedly over-expressed in human pancreatic cancer where it has been found to stimulate growth by an autocrine mechanism [17]. In this review, we will present the evidence that the CCK-B receptor pathway is a key driver of pancreatic carcinogenesis and pancreatic cancer growth. The role of the gastrin /CCK and the CCK-B receptor pathway in other malignancies will also be discussed.

Elevated Blood levels of Gastrin and CCK and Cancer risk

Both gastrin [18] and CCK [19, 20] are trophic hormones and have been recognized for years as important regulators of growth of the GI tract and pancreas, respectively. When gastrin [11] or CCK [12, 13] were applied to pancreatic cancer cells in tissue culture, these peptides were found to significantly increase proliferation of the cancer cells. With the era of gastric acid suppressing proton pump inhibitors (PPIs), a concern has been raised as to whether the elevation of serum gastrin that occurs with these medications [21-24] could indeed increase the risk of pancreatic cancer and other cancers arising from tissues with CCK receptors. A large study of nearly 130,000 patients with *Helicobacter pylori* infections reported an approximate 4-fold increase in colorectal cancers in those with elevated gastrin levels [25]. Numerous studies have now been conducted in subjects such as those with atrophic gastritis, pernicious anemia [26] and Zollinger-Ellison syndrome [27], conditions all associated with markedly elevated gastrin blood levels, and it seems that although hypergastrinemia can increase the risk for enterochromaffin tumors and gastric carcinoids, elevated blood gastrin levels do not appear to act as a carcinogen in and by itself [28] for gastrointestinal adenocarcinomas. However, hypergastrinemia has been shown to increase cancer risk in animal models with precancerous colonic polyps and mutations of the APC gene [29]. Likewise, CCK can increase pancreatic cancer risk if an underlying precancerous lesion exists such as a pancreatic intraepithelial neoplasia (PanIN lesion) [30] and a *KRAS* mutation [30]. And high CCK blood levels from dietary fat have been shown to promote growth of an established pancreatic cancer in animal models [31, 32]. Subjects with chronic pancreatitis, a chronic inflammatory condition, have been shown to have elevated CCK blood levels [33], and these subjects also have an increased risk for the development of pancreatic cancer. These studies in both animals and humans subjects suggest that gastrin and CCK are not mutagenic by themselves; however, these trophic peptides may increase cancer risk when peptide blood levels are elevated in a subject with a precancerous state (i.e., H. pylori, PanINs, colonic polyps) [34] and also stimulate growth of established cancers that possess CCK receptors.

Re-expression of CCK and gastrin and autocrine pancreatic cancer growth

Both gastrin and CCK mRNA and protein expression have been associated with pancreatic cancer. Normal human and porcine pancreas express bioactive amidated gastrins in the embryonic pancreas [15, 35] however, after birth, gastrin immunoreactivity is found only in the G-cells of the gastric antrum [36] and not in the adult pancreas [37]. Although gastrin is not normally expressed in the adult human pancreas [37], it becomes re-expressed in precancerous PanIN lesions [16] and is commonly expressed in human pancreatic cancers where it has been shown to stimulate growth of GI malignancies by an autocrine mechanism [17]. The autocrine mechanism of gastrin stimulating its own growth is substantiated by the finding that endogenous gastrin from cancer cells has been shown to induce its own transcription by activating the CCK- receptor [38]. Thus, pancreatic cells that produce gastrin embryologically become 'silenced' in the normal adult pancreas until a change occurs during carcinogenesis to reactivate its expression. The mechanism involved with the reactivation of gastrin expression is unknown, although there is some evidence that the re-expression may be regulated by microRNAs which are small noncoding RNAs that modulate the expression of mRNA and proteins. Sp-1 or specific protein-1 is a zinc finger transcription factor that binds to GC rich motifs and is often over expressed in cancers including gastrointestinal cancers [39]. A particular miRNA, miRNA-27a, is upregulated in pancreatic cancer [40] and its role has been linked to the down regulation of ZBTB10/RINZF expression: a novel zinc finger protein that inhibits Sp1-dependent activation of the gastrin gene promoter [41]. Gastrin peptide expression is a ubiquitous and important occurrence in pancreatic cancer. When gastrin expression is stably down-regulated with RNA interference in human pancreatic cancer cells, growth of the primary cancer is inhibited and metastases do not occur [42].

CCK is normally produced in the I-cells of the duodenum and not expressed in the pancreas [43]. Gastrin and CCK peptide and their respective mRNA expressions were examined in human pancreatic cancer surgical specimens by radioimmunoassay and RT-PCR [44]. Although high levels of α-amidated gastrins and its precursor were found 74% of the pancreatic tumor specimens, CCK was not detected [44]. Other investigators have, however, reported CCK immunoreactivity in some pancreatic cancer surgical specimens [45]. The role of endogenous CCK peptide expression in pancreatic cancer was examined, and it was found that tumor production of CCK does not influence growth of pancreatic cancer [46] because down-regulation of cancer CCK mRNA rendered effect compared to controls. Hence, both CCK and gastrin peptides may be present in malignant tissue but only the re-expression of endogenous gastrin stimulates pancreatic cancer growth by an auto-

crine mechanism.

Cholecystokinin (CCK) Receptors and Pancreatic Cancer

Two classic types of CCK receptors have been cloned and characterized [47, 48] and these include the CCK-A receptor (previously referred to as the CCK-1R) and the CCK-B receptor (previously referred to as the CCK-2R). The predominant receptor type in the normal murine pancreas is the CCK-A type, while the predominant form in the normal human pancreas is that of the CCK-B variety [49]. In cancerous tissue, however, both CCK-A and CCK-B receptor phenotypes have been described. For example, in a carcinogen induced pancreatic cancer model using azaserine, de novo CCK-B receptors become expressed in the animals that develop cancers [50]. Likewise in the engineered *KRAS* mutant mouse model that spontaneously develops pancreatic cancer through a step-wise progression of dedifferentiated PanIN lesions [51], both CCK-A receptors and the de novo expression of CCK-B receptors are described [52]. Weinburg et al [53] studied the gene expression of CCK receptors in both normal human pancreas tissue and pancreatic cancers. He described only the CCK-B phenotype in normal tissue but expression of both CCK-A and CCK-B receptors in pancreatic cancer [53]. Since some pancreatic cancers possess both types of the CCK receptor, it was unclear if both were functional in mediating the growth stimulatory effects of CCK and gastrin. Experiments demonstrated that in one particular human pancreatic cancer cell line (PANC-1) that expresses both the CCK-A and CCK-B receptors [9, 46], that gastrin or CCK-stimulated cancer growth was mediated only through the CCK-B receptor not the CCK-A receptor [11]. The CCK-B receptor phenotype is the major receptor type in normal human pancreas tissue and present with low abundance; however, The CCK-B receptor increases in number significantly with development of cancer [37].

Several mutations and variations of the CCK-B receptor have been described. Song and colleagues [54] described an area in exon 4 that is alternatively spliced resulting in either a "short or long form" of the receptor with a difference of five amino acids in the 3rd intracellular loop. Smith et al described a novel splice variant of this CCK-B receptor in humans (not murine) with alternative splicing of the entire 4th intron resulting in an additional 69 amino acids to the 3rd intracellular loop [55-57], the portion of the receptor involved in GTP-signal transduction and cell proliferation. This alternative splicing results from a single nucleotide polymorphism (SNP) in position 32 of the 4th intron [58] and occurs only in human cancer cells not in normal tissues; hence the mutated CCK-B receptor containing the translated 4th intron has been termed the "CCK-C" or "CCK-cancer" receptor. Transfection of wild type pancreatic cancer cells with the CCK-C receptor accelerates cell growth in culture [58], whereas, down-regulating this 'mutant' receptor, inhibits growth [59]. In fact, the presence of the SNP for the CCK-C receptor has been reported to occur in up to 40% of patients with pancreatic cancer and its presence was associated with a more aggressive course with shortened survival [60]. Some have suggested that the additional 69 amino acids of the CCK-C receptor render the receptor constitutively active where it induces proliferation in even in the absence of gastrin [61]. This splice variant mRNA expression has been detected by RT-PCR in other cancers including insulinomas, bronchial carcinoids, GIST (gastrointestinal stromal tumors) and small cell lung cancer (SCLC) as well as normal tissues [62]. However, it appears that the genetic SNP may be associated with other cancers since it is a germline mutation expressed in about 11-15% of the normal population, however, expression of the CCK-C receptor protein has only been described thus far in those with pancreatic cancer [58]. A diagram of the CCK receptors and autocrine activation of gastrin is shown in Figure 1.

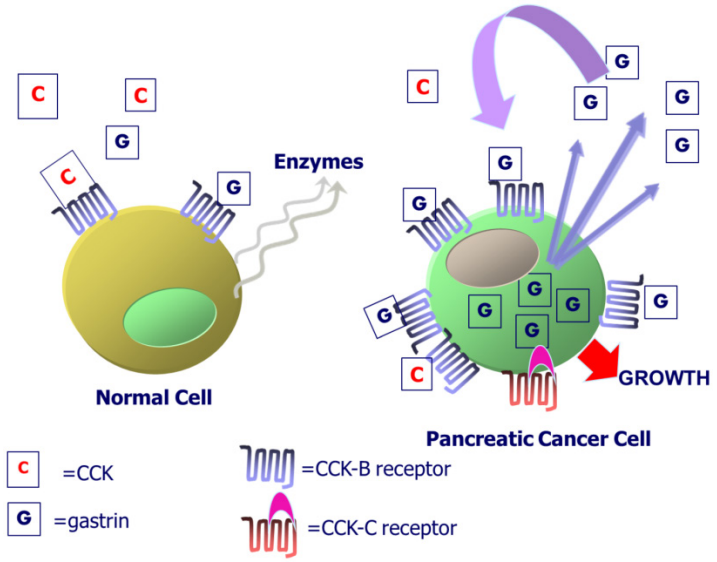

Fig. 1. CCK-B receptors in normal and malignant pancreas cells. Exogenous CCK or gastrin from the peripheral blood binds to the CCK-B receptor in normal human pancreas to activate intracellular signaling and the release of digestive pancreatic enzymes. In pancreatic cancers, the CCK-B receptor is over-expressed and gastrin mRNA and peptide are produced within the cancer cell. Gastrin-17 is released from the cancer cell and binds to the CCK-B receptor to stimulate cell growth by an autocrine mechanism. Some patients with the SNP express a CCK-B spliced variant receptor called the CCK-C receptor that is present only in human pancreatic cancer cells.

The role of the CCK-B receptor in regulating EGFR transactivation in pancreatic cancer cells less well understood. The EGFR was detected on 69% of pancreatic adenocarcinoma tumors examined and 39% of tissues derived from patients with chronic pancreatitis [63]. High glucose promotes pancreatic cancer cellular proliferation by inducing EGF expression and transactivation of the EGFR [64]. In a phase II clinical trial, erlotinib (TKI) with gemcitabine relative to gemcitabine alone significantly decreased the hazard ratio for death and increased the one year survival rate of pancreatic cancer patients [65]. The combination of erlotinib and gemcitabine is approved in Europe for first-line treatment of patients with advanced pancreatic cancer [66]. Erlotinib sensitizes pancreatic cancer cells to AZD8055, a mTOR inhibitor [67]. It remains to be determined if CCK-B receptor antagonists will sensitize pancreatic cancer cells to EGFR TKI.

Intracellular Signaling via the CCK-B receptor

G-protein coupled receptors (GPCRs) like the CCK receptors have been demonstrated to modulate growth of gastrointestinal cancers [68, 69]. In a large pancreatic cancer GWAS analysis, Wei and coworkers [70] screened a database of over 3,000 pancreatic cancer patients and found that the GPCR receptor signaling pathway was the most significant pathway predicting pancreatic cancer risk. When the ligands CCK or gastrin bind and/or activate the CCK-B receptor or the splice variant CCK-C receptor, the receptor undergoes a conformational change that allows exchange of GDP for GTP on the Gα subunit of the heterotrimeric G protein complex. Binding of GTP leads to dissociation of the G protein complex into the Gα subunit and the Gβγ dimer [71]. The GTP-bound Gα subunit then interacts with downstream signaling effectors, leading to activation of various second messenger molecules responsible for eliciting cellular responses including growth, proliferation, differentiation, migration and invasion, angiogenesis, and survival. The Gβγ dimer is also capable of activating PI3K and PLCβ, and acting upon ion channels. When activated by ligand, the CCK receptor signals through Gαq of which there are several subtypes.

We previously demonstrated that down regulation of the CCK-B receptor in pancreatic cancer cells results in apoptosis and halts cell proliferation [72] by interference with intracellular signaling. Gastrin stimulation activates Akt phosphorylation through the CCK-B receptor, [73] and down-regulation of the CCK-B receptor in human pancreatic cancer cells inhibits phosphorylation of Akt [72]. Down regulation of the CCK-B receptor in human PANC-1 pancreatic cancer cells [72] also reduces expression of the X-linked inhibitor of apoptosis protein (XIAP). This factor is typically up-regulated in pancreatic cancer [74, 75, 75] where it binds to active caspase-3 [76, 77] and blocks the increased capase-3 activity induced during apoptosis.

Gastrin activation of the CCK-B receptor, can act in a pro-proliferative manner through the activation of mitogen-activated protein kinases (MAPKs) [including the four sub-groups ERK1/2, JNKs, ERK5, and p38-MAPKs] and cyclins. The ERK1/2 pathway mediates several cellular processes regulated by the CCK-B receptor in enterochromaffin cells, which include proliferation and transcription of gastrin-dependent genes [78]. In CCK-B receptor overexpressing CHO cells or AR42J (rat tumor-derived pancreatic acinar cell line), which endogenously express the CCK-B receptor; gastrin stimulates the ERK1/2 pathway in a protein kinase C dependent manner by tyrosine phosphorylation of Shc, which allow interaction with the Grb2/Sos complex [79-81]. Activation of ERK1/2 in response to gastrin stimulation leads to cellular proliferation and activation of the early response gene c-fos. In gastrointestinal epithelial cells, ERK1/2 activation can involve transactivation of the epidermal growth factor receptor (EGFR), where gastrin induces expression and processing of pro-HB-EGF to EGF and leads to the phosphorylation of EGF receptors and activation of ERK1/2 downstream [82, 83].

CCK receptors and other cancers

CCK receptors have been described and characterized in other GI malignancies including gastric cancer [84, 85] and colon cancers [85-87]. Outside the gastrointestinal tract, both CCK-A and CCK-B receptors are abundantly expressed in lung cancer and binding of CCK or gastrin to small cell lung cancer (SCLC) cells causes elevation of cytosolic Ca^{2+} [88-90]. Although both receptor types are present (as with some pancreatic cancers) it appears that the only the CCK-B receptor is the receptor type involved in malignant cell proliferation since a CCK-B receptor antagonist, CI-988, inhibits SCLC cell growth in vitro and in vivo [91] as well as the ability of CCK-8 to increase cytosolic Ca^{2+}, focal adhesion kinase (FAK), c-fos mRNA, vascular endothelial cell growth factor (VEGF) mRNA.

CCK and gastrin may increase the proliferation of some cancers in an EGFR dependent manner. Using NCI-H727 lung carcinoid cells, CCK-8, CCK-8NS and gastrin-17 significantly increased EGFR tyrosine phosphorylation [91]. Figure 2 shows that the activated CCK-B receptor interacts with Gq activating PLCβ and inducing PI turnover. As a result cytosolic

Ca^{2+} is increased and PKC is activated leading to Src phosphorylation. Src phosphorylates numerous proteins such as FAK, paxillin and PYK-2 altering cancer cellular motility and migration. Src activates MMP which cleaves proTGFα to biologically active TGFα which binds to and activates the EGFR. The EGFR can form homodimers with itself or heterodimers with HER2 causing the phosphorylation of protein substrates such as PI3K [92]. PI3K activates PDK-1, Akt and mTOR leading to cancer cellular survival and or differentiation. The EGFR activates the Ras, Raf, MEK and ERK pathway resulting in altered cellular proliferation. The increase in EGFR and ERK tyrosine phosphorylation caused by addition of CCK-8 to lung carcinoid NCI-H727 cells was significantly inhibited by CI-988, PP2, gefitinib and GM6001, a MMP inhibitor [93]. In gastric epithelial cells, gastrin increases MMP9 expression [94]. CCK-8 stimulated secretion of transforming growth factor (TGF) α, an EGFR ligand, from NCI-H727 cells supporting the important role of CCK-8 in MMP activation. An important finding is that CI-988 and gefitinib are synergistic at inhibiting the proliferation of lung carcinoid cells. The results indicate that GPCR antagonists may synergize with TKI at inhibiting the proliferation of epithelial cancers. In lung cancer, resistance to gefitinib develops primarily due to additional EGFR mutations. It remains to be determined if CCK-B receptor antagonists will increase the sensitivity of gefitinib in cancer cells with additional EGFR mutations.

Therapeutic Strategies to Interrupt the CCK/ Gastrin: CCK-Receptor Pathway in Cancer

Since gastrin is re-expressed in pancreatic cancer and promotes malignant growth in an autocrine mechanism, obvious strategies to down-regulate or block endogenous production of gastrin have been sought. Treatment of pancreatic cancer cells in culture with antisense oligonucleotides to gastrin inhibited cell growth [95]. When gastrin peptide was stably downregulated by RNAi, the subsequent cell clones failed to grow and metastasize in nude mice [42]. In order to deliver siRNAs to cancer cells in vitro, the siRNAs must be protected from degradation by the nucleases in the peripheral blood; therefore, one strategy that is being developed is the packaging of siRNAs in nanoliposomes or nanoparticles. When nanoliposomes loaded with siRNA to gastrin were applied to gastrin-producing BxPC-3 pancreatic cancer cells in culture, gastrin peptide expression by RT-PCR and immunocytochemistry was significantly decreased compared to the same cells treated with a nanoliposomes containing a nonspecific or scrambled control (Figure 3).

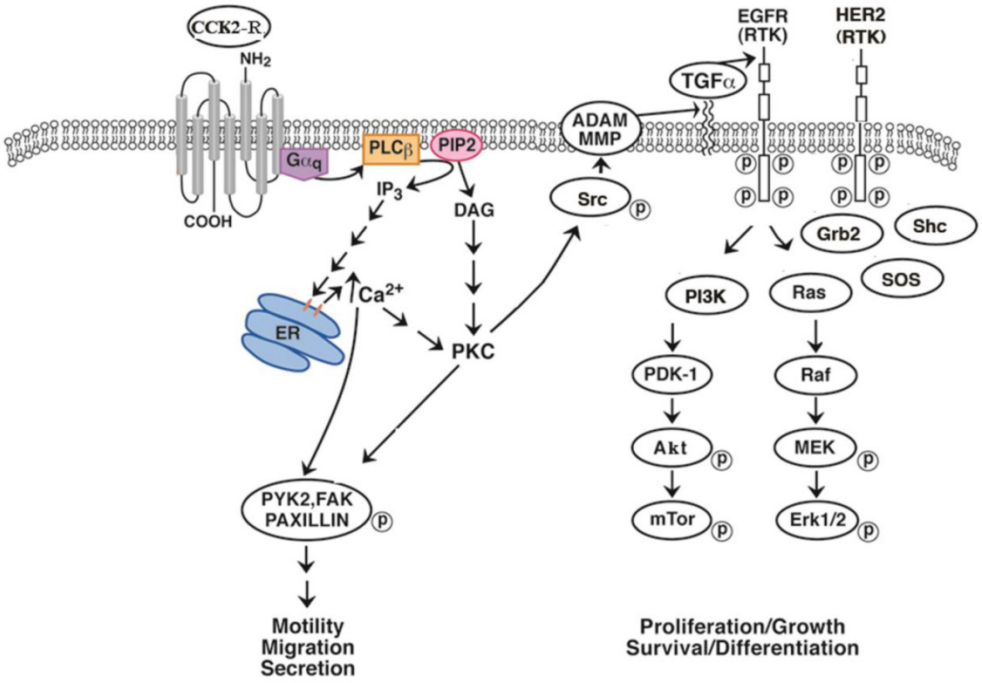

Fig. 2. EGFR transactivation. The CCK-B receptor interacts with Gq causing PLC stimulation and PI turnover. The diacylglycerol and IP_3 released cause PKC activation and elevation of cytosolic Ca^{2+} respectively. PKC causes Src phosphorylation leading to FAK, paxillin and PYK2 phosphorylation. Src affects MMP releasing TGFα from its precursor protein causing EGFR tyrosine phosphorylation. The EGFR phosphorylates PI3K activating PDK1, Akt and mTOR. The EGFR interacts with adaptor proteins Grb2 and SOS activating Ras, Raf followed by phosphorylation of MEK and ERK.

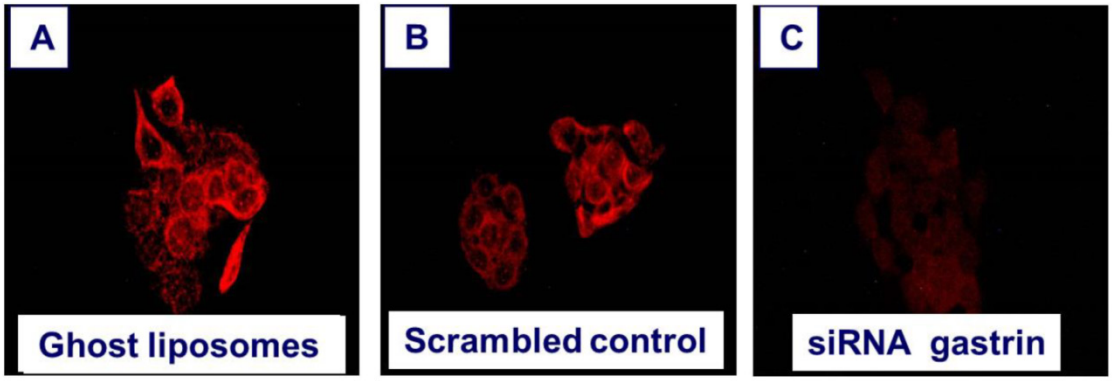

Fig.3. Down regulation of gastrin peptide expression with nanotechnology. Human BxPC-3 pancreatic cancer cells that express high levels of endogenous gastrin were treated for 72 hours with A. nanoliposomes that were empty (ghost) =controls, B. nanoliposomes loaded with a scrambled siRNA =RNA control, or C. nanoliposomes loaded with siRNA specifically directed to gastrin. The cells were washed and reacted with an anti-gastrin antibody (1:500) and secondary goat anti-rabbit AlexaFluor labeled antibody (1:2000), for immunofluorescence analysis of gastrin peptide expression. Immunofluorescent staining was visualized and photographed using Nikon Eclipse upright fluorescent microscope and camera using 40X objective, 2 second exposure and digital zoom of 3.6F. Only the cells treated with nanoliposomes loaded with gastrin siRNA had decreased gastrin immunoreactivity.

Specific gastrin antibodies applied to the culture media of pancreatic cancer cells impairs growth in a dose related fashion [17]. A novel strategy developed by Watson et al [96] involved the raising of an antibody through a vaccine targeted to gastrin called Gastrimmune, or G17DT. This vaccine has a nine amino acid epitope derived from the amino-terminal sequence of gastrin-17 that is conjugated to diphtheria toxoid (DT). The neutralizing ability of rabbit anti-gastrin-17 (G17) antiserum raised by this vaccination was evaluated and found to be effective against colon cancer [96, 97]. G17DT elicited specific and high affinity antibodies that bind gastrin-17, thus preventing its trophic activity. In animals, these antibodies have been shown to reduce the growth and metastatic spread of gastrointestinal tumors [96, 98, 99]. In a randomized placebo controlled clinical study Gilliam and colleagues [100] demonstrated a significant survival benefit in pancreatic cancer patients that elicited neutralizing antibodies toward gastrin in response to vaccination with G17DT. These studies are supportive of the role of gastrin as a key driver in pancreatic cancer growth.

In addition to strategies that neutralize or down regulate gastrin; studies have also been conducted to block the interface with the receptor using CCK- receptor antagonists. More than two decades ago, research in this area of pancreatic cancer therapy was temporarily halted when a clinical study in advanced pancreatic cancer patients with a CCK receptor antagonist failed to demonstrate a clinical benefit [101]. The compound used in this early clinical trial however, (MK-329) was a selective CCK-A receptor antagonist [102]. Since it is now well known that the primary type of receptor that mediates cancer growth in pancreatic cancer in humans is the CCK-B receptor isotype [49], research has been reactivated in this area. Over the past decade numerous highly selective CCK-A and CCK-B receptor antagonists have been developed [103]. The CCK-B receptor antagonist netazepide (YF476) was used to treat patients with type 1 gastric carcinoid tumors [104] and further studies are needed using these more potent and selective antagonists in pancreatic cancer.

Recent studies have shown that inflammation [30, 105] and the conditions of the microenvironment are crucial to carcinogenesis progression. Evidence shows that the CCK receptors may play an important role in PanIN progression and perpetuating the inflammatory milieu of chronic and relapsing pancreatitis[49]. Administration of a CCK analogue, cerulein, has been a classic model for experimental pancreatitis in animals[106] and in the KRAS mouse model administration of exogenous CCK stimulates the CCK receptors and significantly accelerates PanIN progression[30]. The nonepithelial component of the microenvironment in the pancreas has also been shown to play an important role carcinogenesis. These nonepithelial components include activated pancreatic stellate cells, neural factors, endothelial elements, collagen, and inflammatory cells[107]. Berna et al recently described the presence of CCK receptors on pancreatic stellate cells [108] and when these receptors are activated, the stellate cells produce collagen and are responsible for the intense desmoplastic reaction associated with pancreatic cancer [109]. When a non-selective CCK receptor antagonist, proglumide, was added to the drinking water of $KRAS^{G12D}$ transgenic mice, progression of pancreatic intraepithelial neoplasias (PanINs) was arrested and fibrosis reversed [52]. These results support the important role of the gastrin-CCK receptor pathway in pancreatic carcinogenesis and its microenvironment. Furthermore, these data suggest that the use of selective CCK receptor

antagonists may prevent pancreatic cancer development in high risk subjects.

Conclusion

In order to improve the survival of pancreatic cancer, new approaches are needed. Since gastrin is a key driver of pancreatic cancer that stimulates growth through a markedly over-expressed CCK-B receptor, targeting this interface and pathway should have substantial benefits for patient care. Target specific therapies through selective CCK-B receptor antagonist blockade or strategies to down regulate or neutralize the potent trophic effects of gastrin with nanotechnology and immunotherapy show promise in both pancreatic cancers, gastric carcinoid tumors and lung cancers. Lastly a better understanding of the mechanisms involved at the cellular and molecular level of pancreatic cancer will improve our treatment of patients with this lethal disease.

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Competing Interests

The authors have declared that no competing interest exists.

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