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Focal adhesion kinase signaling and function in pancreatic cancer

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TABLE OF CONTENTS

1. ABSTRACT

In the United States and the European Union, pancreatic cancer is the fourth leading cause of cancer death in both men and women. Chemotherapy and radiation therapy have had little impact on survival, prompting the National Cancer Institute to declare that survival for pancreatic cancer has remained unchanged for three decades and its treatment has consistently been identified as an area of unmet medical need. Clearly, additional agents are needed to improve outcomes in this aggressive disease. Clinicians must translate the available knowledge of the molecular basis of this disease into rationale and effective therapeutic strategies for treatment. Pancreatic cancer has been found to have several genetic alterations and is, in fact, one of the tumors with the highest number of genetic mutations of any solid malignancy. These mutations include activation of K-ras and inactivation of p53, p16, and DPC4. Other alterations include upregulation of angiogenic factors and matrix metalloproteinases, dysregulation of growth factor receptors, and cytoplasmic kinases including focal adhesion kinase (FAK) and Src. The role of FAK in the pathogenesis of pancreatic cancer is discussed below and efforts aimed at the development of inhibitors of FAK for this disease are reviewed.

2. INTRODUCTION

The pancreatic ducts are one of the most common sites of human neoplasia, affecting nearly half of the elderly population (1-3). Just as multiple adenomas can occur within the colorectum of an individual, multiple independent benign pancreatic neoplasms tend to be present simultaneously. Only about 1-in-500 intraductal neoplasms progresses to cancer, and appears to do so through a series of progressive lesions (4). The tumor progression model for pancreatic neoplasia therefore follows closely upon the model established for colorectal tumors.

Molecular studies of pancreatic duct carcinomas have revealed that this cancer is associated with several genetic mutations. Current genetic profiles of pancreatic cancer suggest these tumors contain amongst the highest number of gene mutations, per tumor, for any human system known. These mutations include very frequent mutations of the K-ras gene leading to its activation, inactivation of the p16 gene, as well as common inactivations of the p53 and DPC4 genes (5-7). Other alterations that occur in pancreatic cancer include deregulation of growth factors and growth factor receptors,

matrix metalloproteinases and regulators of tumor angiogenesis. In addition, amplification of genes from the 8q, 11q, 17q and 20q chromosome arms is common in pancreatic cancer (8).

It is clear that novel molecular targets and strategies need to be developed for the treatment of pancreatic cancer. Several agents targeting a variety of pathways are in early clinical testing in pancreatic cancer and include those directed at Src and FAK. Src was the first reported proto-oncogene and encodes a nonreceptor tyrosine kinase with involvement in the regulation of proliferation, differentiation, survival, motility, angiogenesis, and cell-cell interactions. Malignant Src activity is related to the overexpression of the wild-type protein rather than expression of a mutated genotype. Src has been demonstrated to phosphorylate FAK on multiple residues and increase FAK kinase activity. Src activity may contribute to both constitutive and EGF-induced VEGF expression and, therefore, to angiogenic potential. This has been shown in pancreatic cancer cells *in vitro* and in animal models growing human pancreatic tumors (9). Src inhibitors are in phase 1 and 2 clinical testing and clinical trials combining an oral Src inhibitor with gemcitabine are in progress (10).

FAK is a cytoplasmic protein tyrosine kinase that, as its name suggests, is localized to focal adhesions, which are contact points between a cell and its ECM. Tyrosine phosphorylation of FAK occurs in response to the clustering of integrins, during formation of focal adhesions and cell spreading, and upon adhesion to fibronectin (11-15). FAK does not function as a classic oncogene, affecting cell transformation. Rather, it promotes a more invasive and metastatic phenotype of an established malignancy. FAK appears to have many functions in cells, linking integrin signaling to downstream targets, (16, 17) acting as part of a survival signal pathway, (18, 19) and having a connection with cell motility (20, 21). FAK is phosphorylated following activation of a number of transmembrane receptors (22). FAK functions not only as a kinase, but also as a scaffolding protein for the assembly of a number of cellular signaling molecules, suggesting that FAK is a critical mediator of cell-ECM signaling events.

FAK has been shown to be strongly expressed in multiple pancreatic cancer cell lines at the levels of mRNA, protein and phosphorylated protein (23). Our laboratory group has played an important role in defining the biology of FAK in pancreatic cancer. We have demonstrated in pancreatic cancer cells, as well as *in vivo* models, that FAK inhibition is an effective antineoplastic strategy by inducing apoptosis and sensitizing tumor cells to chemotherapy (24-26). A FAK inhibitor is currently in phase 1 testing (27, 28).

3. IN VITRO STUDIES OF FAK INHIBITION IN PANCREATIC CANCER CELLS

Sawai and colleagues have demonstrated that FAK plays a critical role in adhesive behavior of pancreatic cancer cells via activating the Ras/ERK signaling pathways. In their studies, FAK protein association with beta-1 integrin was increased when cells were attached on type 4 collagen and a further increase was observed by stimulation with IL-1-alpha. Furthermore, knockdown of FAK expression with siRNA inhibited IL-1-alpha induced Ras/ERK activation with subsequent inhibition of IL-1-alpha-induced adhesion and invasion of pancreatic cancer cells (29).

In addition, to FAK's effects on signaling through Ras/ERK, increased PI3-K/Akt pathway activity is reported following FAK overexpression (30) and FAK inhibition has been shown to decrease AKT activity. Duxbury and colleagues tested the effect of suppressing FAK expression with siRNA on the proliferation of Panc-1, Miapaca-2 and BxPC3 pancreatic cancer cells in culture. Although FAK knockdown was not complete with siRNA, treatment with FAK siRNA did not induce any change in the doubling time of these cells. In addition, in attached cells growing in monolayer culture, there was no statistically significant difference in the apoptotic fraction or caspase 3 activity between cells treated with FAK siRNA vs control siRNA. However, siRNA to FAK did decrease Akt kinase activity in Miapaca-2 cells (31). Furthermore, FAK gene silencing was shown to potentiate gemcitabine-induced caspase mediated apoptosis in three pancreatic cancer cells lines possibly due to its effects on Akt kinase activity. Since activation of Akt is common in pancreatic adenocarcinoma and Akt inhibition has been shown to induce chemosensitization in pancreatic adenocarcinoma cells, FAK gene silencing may exert its effects through inhibition of Akt activity.

The ability of FAK knockdown with siRNA to induce apoptosis in pancreatic cancer cells has also been determined in anchorage independent conditions. In the absence of anchorage, sixteen-hour polyHEMA culture induced significant increases in the anoikis fractions and decreased viability of Miapaca-2, Panc-1, BxPC3 and Capas2 cells. The increase in the anoikis fraction after siRNA to FAK was associated with a significant increase in caspase activities (32).

One of the major reasons for the poor prognosis of pancreatic cancer is its high resistance to currently available chemotherapeutic agents. Huanwen and colleagues have nicely demonstrated that the level of constitutive phosphorylation of FAK at Tyr397 correlated with the extent of intrinsic resistance to gemcitabine in four pancreatic cancer cell lines (Figure 1). Moreover, in Panc-1 cells, which have a high expression of p-FAK, specific inhibition of constitutive FAK phosphorylation by either RNAi or dominant negative FRNK overexpression decreased the phosphorylation of Akt, reduced the levels of survivin expression and Bad phosphorylation at Ser136 and increased gemcitabine induced cytotoxicity and apoptosis. However, in AsPC-1 cells with a low level of p-FAK, neither FAK RNAi nor FRNK overexpression affected gemcitabine induced cell apoptosis. Furthermore, these findings were supported with the use of a PF-573,228, a novel FAK inhibitor which blocks FAK phosphorylation and targets FAK catalytic activity (33)

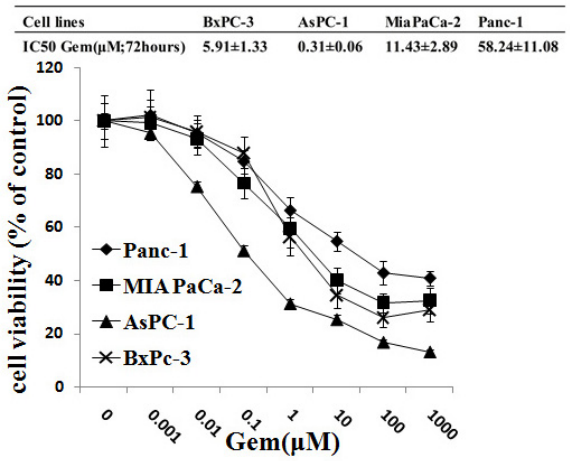

Figure 1. The cell viability of BxPC-3, AsPC-1, Mia-PaCa-2 and Panc-1 cells was determined by MTT assay after treatment with increasing doses of Gemcitabine for 72 hours. Cells with higher levels of constitutive pFAK (pY397) showed higher intrinsic chemoresistance to Gemcitabine treatment. Reproduced with permission from (33).

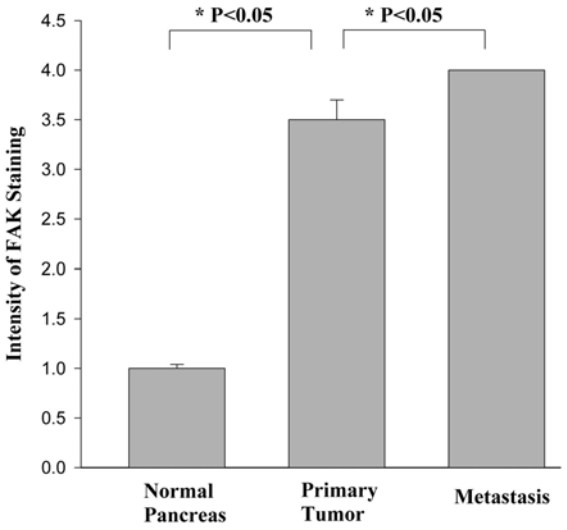

Figure 2. FAK expression in normal pancreas and primary and metastatic pancreatic adenocarcinoma. Immunohistochemical staining of FAK in (A) normal pancreas (n=10), (B) primary pancreatic adenocarcinoma (n=13), and (C) metastases (n=16). Intensity of FAK staining is higher in pancreatic carcinoma than in normal pancreas, and higher in metastases than in primary tumor (mean $\pm$ SE: normal pancreas: 1.0$\pm$0.04; primary tumor: 3.5$\pm$0.2; metastasis: 4$\pm$0, $p<0.05$). Reproduced with permission from (26).

Since the Y397 autophosphorylation site is important for FAK survival function, recently our laboratory has performed computer and functional modeling approaches and identified a novel small molecule inhibitor of FAK function targeting the Y397 autophosophorylation site of FAK. This site is important for FAK survival function and binds several important signaling proteins. We found that 1,2,4,5-Benzenetetraamine tetrahydrochloride, called Y15, specifically targets the Y397 site of FAK, directly and specifically decreases Y397-phosphorylation of FAK *in vitro*, inhibits pancreatic cancer cell viability, causes detachment, decreases cell adhesion and Y397 FAK autophosporylation in pancreatic cancer cells. In addition, the combination of gemcitabine (10 uM) chemotherapy + Y15 (10 uM) treatment significantly decreased cell viability compared to gemcitabine (10 uM) or Y15 treatment (10 uM) alone (24).

4. ASSOCIATION OF FAK WITH OTHER TYROSINE KINASES IN PANCREATIC CANCER

The N-terminal domain of FAK has been shown to associate with beta subunit of integrin and growth factors (13, 15, 34), implying the important role of FAK in integrating diverse cellular signaling pathways. Recently, we have demonstrated by a series of pull-down assays using GST-tagged FAK fragments and His-tagged IGF-1R intracellular fragments, that the FAK-NT2 (aa 127-243) domain directly interacts with the N-terminal part of the IGF-1R intracellular domain (35). In addition, in pancreatic cancer cells, we have previously demonstrated co-immunoprecipitation of FAK and IGF-1R and colocalization of these two proteins utilizing confocal microscopy. Furthermore, utilizing multiple inhibitors of IGF-1R (dominant negative and kinase inhibitors) and FAK (dominant negative, siRNA and kinase inhibitor) we have shown that inhibition of the activity of both tyrosine kinases resulted in a synergistic decrease in cell proliferation, increase in cell detachment and increase in apoptosis in pancreatic cancer cells. The mechanism for this synergistic effect appears to be through pathways that involve ERK and Akt since both p-ERK and p-Akt were decreased following dual inhibition of FAK and IGF-1R (25). With the administration of a kinase inhibitor (TAE226) that targets both FAK and IGF-1R catalytic activity we have also shown inhibition of *in vitro* and *in vivo* tumor growth in pancreatic cancer (25, 26).

5. IN VIVO STUDIES OF FAK INHIBITION IN PANCREATIC CANCER

FAK has been shown to be present in abundance in human pancreatic tumors (23, 36). Data from our laboratory has shown increased expression of FAK in human pancreatic cancers as they progress from normal pancreas to adenocarcinoma and subsequently to metastases (26) (Figure 2). Therefore, FAK appears to be a valid target in pancreatic cancer.

Of interest, investigators have shown that FAK gene silencing inhibits metastasis in a nude mouse model of orthotopic pancreatic cancer. Of the mice that were injected with pancreatic cancer cells that had been treated *ex vivo* with siRNA, none of the mice developed metastatases compared to 60-100% of mice treated with control siRNA (32)

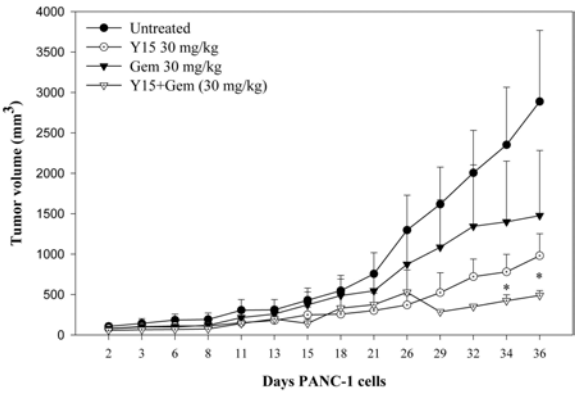

Figure 3. Y15 significantly blocks tumor growth *in vivo* and its effects are synergistic with gemcitabine treatment. Mice (n = 5/group) were subcutaneously injected with Panc-1 cells. The day after injection, mice were treated with daily intraperitoneal PBS, intraperitoneal Y15 (30 mg/kg), intraperitoneal gemcitabine alone (30 mg/kg) or Y15 (30 mg/kg) + gemcitabine (30 mg/kg). The combination of Y15 + gemcitabine significantly decreased tumor volume compared to Y15 or gemcitabine (Gen) alone. *p < 0.05 vs. Y15 or gemcitabine alone. Reproduced with permission from (24).

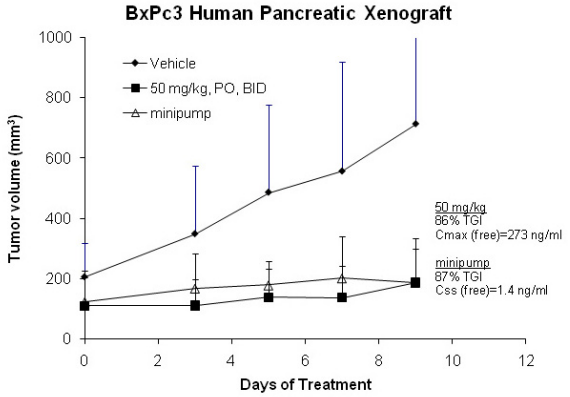

Figure 4. Tumor growth inhibition with PF-562,271 of BxPc3 xenografts. Mini-pumps, which continuously deliver compound for the entire dosing period, generated comparable tumor inhibition as 50 mg/kg twice daily. Cmax is ng/mL free fraction. Css, steady state concentration. Reproduced with permission from (37).

The efficacy of FAKsiRNA as an *in vivo* chemosensitizing strategy has been tested in an orthotopic xenograft model of pancreatic cancer. Contrary to the *in vitro* findings where FAK siRNA did not affect the cellular proliferation in monolayer culture, FAK siRNA did suppress tumor growth in the nude mouse. Mice treated with gemcitabine in combination with FAK siRNA had a 75% tumor growth inhibition compared to mice treated with gemcitabine alone or mice treated with gemcitabine and control siRNA (31).

We have demonstrated that a novel molecule (1,2,4,5-Benzenetetraamine tetrahydrochloride), that targets the Y397 autophosphorylation site of FAK, blocks tumor growth *in vivo*. In further support of the ability of FAK inhibition to increase chemosensitization in pancreatic malignancy, our lab has demonstrated that the combination of Y15 + gemcitabine treatment significantly inhibited tumor growth compared to either one alone (Figure 3). In addition, combined treatment with Y15 + gemcitabine caused a significant decrease in tumor weight compared to the other groups (24). Thus, targeting the Y397 site in pancreatic cancer may be an effective approach for developing future FAK-targeted therapeutics.

Recently, Pfizer has developed and published pre-clinical results with PF-562,271 which is a potent, ATP-competitive, reversible inhibitor of FAK and Pyk2 catalytic activity with a IC50 of 1.5 and 14 nmol/L, respectively. PF-562,271 showed robust antitumor activity as a single agent in multiple tumor types including a mouse model of BxPC3 human pancreatic xenografts when delivered orally at 50 mg/kg twice a day (Figure 4). PF-562,271 was very well-tolerated with no decrease in animal weight or activity (37).

6. SIGNIFICANCE OF FAK EXPRESSION IN PANCREATIC CANCER

There are limited studies which have evaluated the prognostic significance of FAK expression in human specimens of pancreatic adenocarcinoma. In a study from the University of Athens, FAK protein expression was assessed immunohistochemically in tumor specimens from 65 patients with pancreatic adenocarcinoma and correlated significantly with the T stage of the tumor (p=0.037). In addition, the intensity of FAK immunostaining correlated significantly with the age of the patients (p=0.030), the tumor differentiation grade (p=0.041) and the presence of distant metastases (p=0.029). However, FAK expression and intensity of staining did not correlate with survival (36). In another study from Japan, FAK protein expression was determined immunohistochemically in 50 patients with resected pancreatic adenocarcinoma. There was a significant correlation between FAK expression and tumor size. However, FAK expression did not significantly correlate with other factors such as grade, lymph node metastases, or survival. These results suggest that greater tumor size may be associated with an increased rate of cell proliferation and FAK expression. FAK expression may not be a prognostic marker for pancreatic cancer patients but may represent a molecular target for therapeutic intervention in these patients (23).

7. HUMAN STUDIES

Phase I clinical trials utilizing the FAK kinase inhibitor, PF-562,571, in several tumor types have been completed and phase II studies are ongoing. The results of an initial phase 1 dose-escalation study of PF-562,271 given as twice daily oral doses in 21 day cycles was reported in 2007 (27). Endpoints included safety, tolerability, PK, PD (serial tumor biopsies) and antitumor activity. Although no patients with pancreatic adenocarcinoma were treated in this study, 32 patients with

advanced solid tumors received from 5 mg up to 105 mg BID. Nine patients tolerated over 3 cycles and another 4 patients continued treatment over 6 cycles with stable disease. At 105 mg BID, dose- limiting toxicities included nausea, vomiting, and diarrhea. The conclusion from this study is that at the doses evaluated, PF-562,271 is tolerable with extended BID oral administration.

In a study that included a limited number of patients with pancreatic malignancy, the results of a phase 1 dose escalation study of PF-562,271 given as continuous oral dosing in 21 day cycles, was reported in 2010 (28). Approximately 100 patients with different tumor types received doses ranging from 5 mg to 105 mg BID or 125 mg to 225 mg QD without food, or 100 mg to 150 mg BID with food. The demographics of the patients included a median age of 60 years (range 25-83) and the primary tumor sites were colorectal in 21, pancreatic in 15, head and neck in 13, lung in 7, breast in 5, prostate in 5, sarcoma in 5, ovary in 3, and others in 25. Treatment with PF-562, 271 was tolerable for 6-12 months in some patients with sustained disease control. The clinical safety and antitumor activity support further development of this and other FAK kinase inhibitors.

8. PERSPECTIVE

Pancreatic cancer is an aggressive tumor with limited treatment options. FAK is upregulated and strongly expressed in pancreatic cancer cells at the level of mRNA, protein and phosphorylated protein. Human pancreatic cancer expression of FAK has been shown to correlate with increasing tumor size and aggressive behavior. FAK knockdown with siRNA and FAK kinase inhibition has antitumor activity. FAK protein expression correlates with sensitivity to gemcitabine chemotherapy and inhibition of FAK activity potentiate the effect of gemcitabine chemotherapy. Clinical trials of FAK inhibition in multiple tumor types are underway and may give insight to novel treatment approaches in patients with pancreatic cancer.

9. ACKNOWLEDGMENTS

All authors contributed equally to this article.

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