Regulatory role of c-Met in insulin-like growth factor-I receptor–mediated migration and invasion of human pancreatic carcinoma cells

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Abstract
Pancreatic carcinoma cells overexpress the insulin-like growth factor-I (IGF-I) receptor (IGF-IR) and the hepatocyte growth factor (HGF) receptor, c-Met, which are both known to mediate tumor cell migration and invasion. We hypothesized that IGF-IR and c-Met cooperate to induce migration and invasion of human pancreatic carcinoma cells and that IGF-I-mediated migration and invasion depend on c-Met. Migration and invasion assays were done with the human pancreatic cancer cell line L3.6pl treated with PBS, IGF-I, HGF, or IGF-I plus HGF. To determine if c-Met is necessary for IGF-IR-mediated migration and invasion, c-Met was down-regulated in L3.6pl cells via adenoviral infection with a c-Met ribozyme before IGF-I treatment. IGF-I and HGF increased cell migration and invasion. Furthermore, IGF-I plus HGF had a greater than additive effect on cell migration and invasion compared with either growth factor alone. Down-regulation of c-Met nearly completely inhibited IGF-I-mediated migration and invasion. Our findings suggest that IGF-IR and c-Met cooperate to induce migration and invasion of human pancreatic carcinoma cells. Furthermore, c-Met is required for both HGF- and IGF-I-mediated migration and invasion. Elucidation of the signaling pathways that contribute to tumor progression and metastasis should provide a foundation for the development of targeted therapies for pancreatic carcinoma. [Mol Cancer Ther 2006;5(7):1676–82]

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Introduction
Pancreatic adenocarcinomas are highly aggressive tumors, and patients with this malignancy have a 5-year overall survival rate of only 4% (1). Even in patients with apparently localized, resectable disease, the 5-year overall survival rate is only 21% (2). More effective therapies for pancreatic carcinoma are thus needed.

Insulin-like growth factor-I (IGF-I; refs. 3-13) and its receptor, IGF-I receptor (IGF-IR), and hepatocyte growth factor (HGF)/scatter factor (14-18) and its receptor, c-Met, have been implicated in the development and progression of a variety of human cancers, including pancreatic adenocarcinoma. IGF-I/IGF-IR signaling (19-23) and HGF/c-Met signaling (12, 18, 24-27) are important mediators of tumor cell migration and invasion. However, the pathways by which these factors induce tumor cell migration and invasion have not been fully elucidated. Cooperation between various receptors and their signaling pathways is important in regulating cellular responses. Examples include cooperation between the tyrosine kinase receptor Ron and the epidermal growth factor receptor (28), between IGF-IR and epidermal growth factor receptor (29), between the estrogen receptor and IGF-IR (30), and between G protein-coupled receptors and IGF-IR (31).

Although cooperation between IGF-IR and c-Met in human pancreatic carcinoma cells has not been shown previously, evidence suggests that such cooperation is likely. First, IGF-I signaling in breast carcinoma (5, 20) and HGF signaling in various malignancies (24, 32, 33), including pancreatic carcinoma (12), result in activation of a common downstream mediator of invasion, the urokinase plasminogen activator/urokinase plasminogen activator receptor system; urokinase plasminogen activator has been shown to cleave pro-HGF to active HGF (34). Second, IGF-I signaling induces hypoxia-inducible factor-1α in pancreatic carcinoma cells (11), and hypoxia, likely through this factor, has been shown to increase c-Met levels in human lung, hepatocellular, and other carcinomas (35). Third, growth factor receptor binding protein 2-associated binder-1, which is the main substrate and docking protein regulating downstream signaling by c-Met, has also been shown to function as a signaling intermediate for IGF-I (36). Fourth, IGF-I and HGF have been shown to function as comitogens in a rat hepatoma cell line (37).

We therefore hypothesized that IGF-IR and c-Met cooperate to induce migration and invasion of human pancreatic carcinoma cells. IGF-I-mediated migration and invasion depend on c-Met. In the current study, we used a c-Met ribozyme to down-regulate c-Met function in L3.6pl human pancreatic carcinoma cells and then treated cells with PBS, IGF-I, HGF, or IGF-I plus HGF.
and did Transwell migration and invasion assays. We found that IGF-I and HGF cooperated to induce migration and invasion. Down-regulation of c-Met function showed that c-Met was critical for HGF- and IGF-I-induced migration and invasion. The identification of cooperation between the growth factors IGF-IR and c-Met in human pancreatic carcinoma is novel.

**Materials and Methods**

**Cell Lines and Cell Culture Conditions**

The human pancreatic carcinoma cell line L3.6pl (38) was kindly provided by I.J. Fidler, D.V.M., Ph.D. (The University of Texas M. D. Anderson Cancer Center, Houston, TX). Cells were cultured and maintained in MEM supplemented with 10% fetal bovine serum, 2 units/mL penicillin-streptomycin mixture (Flow Laboratories, Rockville, MD), vitamins (Life Technologies, Inc., Grand Island, NY), 1 mmol/L sodium pyruvate, 2 mmol/L L-glutamine, and nonessential amino acids in 5% CO2-95% air at 37°C.

**Transwell Migration and Invasion Assays**

For assessment of cell migration *in vitro*, L3.6pl cells (1.5 × 10^5 in 500 μL MEM supplemented with 1% fetal bovine serum) were placed in the upper chamber of Transwell migration chambers (8-μm BioCoat control inserts, Becton Dickinson Labware, Bedford, MA). The lower chamber was filled with 750 μL MEM supplemented with 10% fetal bovine serum plus one of the following: (a) PBS, (b) recombinant human IGF-1 (100 ng/mL; R&D Systems, Minneapolis, MN), (c) recombinant human HGF (100 ng/mL; R&D Systems), or (d) IGF-I plus HGF (100 ng/mL each). After 24 hours, unmigrated cells were removed from the upper surface of the Transwell membrane with a cotton swab, and migrated cells on the lower membrane surface were fixed, stained, photographed, and counted under high-power magnification.

For assessment of invasion, *in vitro* invasion assays were done under the same conditions as the Transwell migration assays but in Matrigel-coated Transwells (BioCoat Matrigel invasion chamber, Becton Dickinson Labware). Transwell migration and invasion assays were done in triplicate.

**Scratch Wound Assay**

To verify the results of the Transwell migration assays, a scratch wound assay was done. L3.6pl cells were grown to confluence in 10% MEM on four 100-mm cell culture dishes (Corning, Inc., Corning, NY), and the medium was changed to 1% MEM overnight. The plates were then scratched linearly in multiple areas with a cell scraper (Costar 3010, Corning). Fresh 1% MEM was then added to each plate plus one of the following: (a) PBS, (b) IGF-I (100 ng/mL), (c) HGF (100 ng/mL), or (d) IGF-I (100 ng/mL) plus HGF (100 ng/mL). The medium was changed and supplemented with the specified cytokines daily.

Photographs were taken of each plate at four marked locations under ×10 magnification immediately after wounding for baseline wound measurement (t₀) and again at 12, 24, and 36 hours after wounding. The wound area was calculated for each image using image analysis software (Scion Image, Beta 4.0.2, Scion Corp., Frederick, MD). The percentage wound coverage (i.e., percentage decrease in wound area relative to t₀) was calculated for each wound at each time point, and the mean percentage wound coverage was determined for the four wounds in each group at each time point.

**Down-Regulation of c-Met with Ribozyme-Expressing Adenovirus**

The c-Met ribozyme (39), designed to down-regulate c-Met expression, was the kind gift of John Laterra, M.D., Ph.D. (John Hopkins University School of Medicine, Baltimore, MD). The c-Met ribozyme contains U1snRNA, a 41-bp c-Met antisense sequence, and a hammerhead ribozyme that targets c-Met mRNA at bp 560. The control plasmids lack the ribozyme and the c-Met targeting sequence but contain the U1snRNA and other plasmid sequences. An adenovirus expressing the ribozyme (ad-c-Met ribozyme) and a control adenovirus (ad-pU1) were harvested and purified as described previously (40, 41). A BLAST search (RIF: 1128110381-14707-51187997922.BLASTQ1) was done on the National Center for Biotechnology Information Transcript Reference Sequences database to search for all possible human sequences with significant alignment with the 41-bp mRNA antisense sequence used in the ribozyme construct. The human c-Met mRNA was the only sequence that produced significant alignment with the antisense sequence. The unique specificity of this c-Met ribozyme has been confirmed and published previously (39, 40).

**Western Blot Analysis for c-Met, Total IGF-IR and Phosphorylated IGF-IR**

To determine the effect of the c-Met ribozyme, total c-Met and IGF-IR protein levels were measured by Western blot analysis. L3.6pl cells at 80% confluence were infected with ad-c-Met ribozyme or ad-pU1 (control) at 50 multiplicities of infection. After 24 hours, cells were lysed with lysis buffer [50 mmol/L HEPES (pH 7.0), 150 mmol/L NaCl, 1.5 mmol/L MgCl₂, 1 mmol/L EDTA, 10 mmol/L sodium pyrophosphate, 10% glycerol, 1% Triton X-100, 1 mmol/L sodium orthovanadate, 1 complete Mini protease inhibitor cocktail tablet (Roche Diagnostics, Basel, Switzerland)]. The proteins (50 μg) were separated by SDS-PAGE and transferred to polyvinylidene difluoride membranes (Immobilon-P transfer membrane, Millipore Corp., Bedford, MA). Following blocking with 5% milk in TBS/0.1% Tween 20 (v/v), the membranes were probed with anti-c-Met antibody (1:1,000 in 5% milk) [met (C-28), Santa Cruz Biotechnology, Santa Cruz, CA] or anti-IGF-IRβ antibody (1:200 in 5% milk; IGF-IRβ (C-20), Santa Cruz Biotechnology]. The membranes were then washed and treated with horseradish peroxidase–conjugated goat anti-rabbit IgG (1:3,000 in 5% milk; Bio-Rad Laboratories, Hercules, CA). Immunoreactive proteins were visualized with an enhanced chemiluminescence detection kit (Amersham Biosciences, Little Chalfont, United Kingdom). β-Actin (Sigma-Aldrich Corp., St. Louis, MO) was used as a loading control. To evaluate the effect of ad-c-Met ribozyme on IGF-IR phosphorylation, L3.6pl cells were grown to 80%...
confluence, infected with ad-pU1 or ad-c-Met ribozyme as described above, and then treated with PBS or IGF-I (100 ng/mL) for 24 hours. Cellular protein was extracted, and Western blotting was done as described above using an antibody to phosphorylated IGF-IR (1:1,000 in 5% milk; Tyr1131, Cell Signaling Technology, Danvers, MA).

The effects of IGF-I and HGF treatment on total and phosphorylated c-Met expression were determined in L3.6pl cells in triplicate. Cells were treated, cellular protein was extracted, and Western blotting was done as described above using the anti-c-Met antibody as well as a phosphorylated anti-c-Met antibody (1:1,000 in 5% milk).

**c-Met Immune Complex Kinase Assay**

To determine the degree of inhibition of the c-Met ribozyme on c-Met kinase activity, the c-Met immune complex kinase assay was done in duplicate as described previously (40–42). Briefly, c-Met was immunoprecipitated from 500 μg total cellular protein in 500 μL lysis buffer (detailed above) with 1 μg anti-c-Met antibody and rotated at 4°C for 12 hours. Immune complexes were formed with the addition of 50 μL of 10% (v/v) formalin-fixed *Staphylococcus aureus* (Pansorbin, Calbiochem, San Diego, CA) and rotated at 4°C for 4 hours. Kinase reactions were initiated at room temperature with the addition of kinase reaction buffer (20 mmol/L HEPES, 100 mmol/L sodium orthovanadate, 10 mmol/L MnCl2, 10 mmol/L MgCl2, 10 μCi [γ-32P]ATP) plus 10 μg acid-denatured rabbit muscle enolase (Sigma-Aldrich) After 10 minutes, reactions were terminated by the addition of SDS sample buffer. Proteins were separated by 8% SDS-PAGE, the gel was dried, and radioactive bands were detected by autoradiography.

**Cell Counts by 3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide Assay**

3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assays were done to evaluate the effects of IGF-I, HGF, and IGF-I plus HGF on survival of L3.6pl cells and to assure that any increase in cell migration or invasion was not simply due to an increase in cell number. Cells (1.5 × 10^5) were plated in 96-well plates in 1% fetal bovine serum–containing MEM (initial conditions in upper chamber of Transwells) or 6% fetal bovine serum–containing MEM (representing equilibrated conditions between the upper and lower chambers of the Transwells); PBS, IGF-I, HGF, or IGF-I plus HGF was added to achieve a final concentration of 100 ng/mL. Assays were done in quadruplicate. After 24 hours, 2 mg/mL MTT (Sigma-Aldrich) in PBS was added (50 μL/well), and plates were incubated at 37°C for 2 hours. Medium and MTT were removed, dimethyl sulfoxide was added for 10 minutes, and absorbance was measured at 570 nm. For each of the MTT assays, the conditions of the migration and invasion assays were replicated: the cells were kept under the same culture conditions, plated at the same cell density, and treated for the same period with the same dose of IGF-I and/or HGF.

**Statistical Analyses**

Statistical analyses were done using InStat 3.01 software (GraphPad Software, Inc., San Diego, CA). The significance

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**Figure 1.** Effect of IGF-I and HGF on pancreatic carcinoma cell migration. **A**, a Transwell migration assay was done on L3.6pl cells with PBS, IGF-I, HGF, or IGF-I plus HGF (IGF-I + HGF). After 24 h, migrated cells were fixed, stained, and counted. IGF-I and HGF significantly increased cell migration; the effects of IGF-I plus HGF were more than additive. Representative photographs are migrated cells. Columns, mean of 10 high-power fields (HPF); bars, SE. *, P < 0.001 versus PBS. **B**, a scratch wound assay was done. Wounds were made on plates of confluent L3.6pl cells followed by the addition of medium supplemented with PBS, IGF-I, HGF, or IGF-I plus HGF. Wounds were photographed and measured at 0 (t₀), 12, 24, and 36 h after wounding. Cell migration was assessed as percentage wound coverage over time. Representative photographs are wounds. **C**, percentage wound coverage. IGF-I and HGF increased cell migration, and IGF-I plus HGF had a greater than additive effect. Points, mean of four wounds; bars, SE. *, P < 0.05 versus PBS; **, P < 0.005 versus PBS.
of differences between treatment groups and control groups was determined using the Mann-Whitney U test, Student's t test, or Fisher's exact test, as appropriate. Significance was determined with 95% confidence interval.

Results

Effect of IGF-I and HGF on Cell Migration and Invasion

Transwell migration assays were done to evaluate the effect of IGF-I and HGF on L3.6pl cell migration. IGF-I led to a mean 10 ± 1–fold (±SE) increase in cell migration (P < 0.0001 versus PBS), and HGF led to a mean 46 ± 2–fold increase in cell migration (P < 0.001 versus PBS; Fig. 1A). The combination of IGF-I plus HGF led to a mean 72 ± 3–fold increase in cell migration (P < 0.0001 versus PBS; Fig. 1A), which was significantly greater than the mean increase with IGF-I or HGF alone (P < 0.0001).

To confirm the effects of IGF-I and HGF on cell migration, we did a scratch wound assay. The PBS-treated cells (controls) showed very little migration, resulting in a mean of 3 ± 5% wound coverage at 36 hours. By 36 hours, IGF-I treatment led to a mean of 29 ± 2% wound coverage (P < 0.005 versus PBS), HGF treatment led to a mean of 40 ± 11% wound coverage (P < 0.05 versus PBS), and treatment with IGF-I plus HGF led to a mean of 82 ± 10% wound coverage (P < 0.005 versus PBS; Fig. 1B and C), which was greater than the mean increase with IGF-I or HGF alone (P < 0.05).

The effect of IGF-I and HGF on L3.6pl cell invasion was evaluated using Matrigel-coated Transwell invasion assays. IGF-I led to a mean 28 ± 2–fold increase in cell invasion (P < 0.0001 versus PBS), and HGF led to a mean 31 ± 4–fold increase in cell invasion (P < 0.0001 versus PBS; Fig. 2). The combination of IGF-I and HGF led to a mean 114 ± 11–fold increase in cell invasion (P < 0.0001 versus PBS; Fig. 2), which was significantly greater than the mean increase with IGF-I or HGF alone (P < 0.0001).

To show that the increases in cell migration and invasion were not due to increases in cell number induced by IGF-I and HGF, we did an MTT assay on L3.6pl cells treated with PBS, IGF-I, HGF, or IGF-I plus HGF. There was no increase in cell number in any of the treatment groups after 24 hours (data not shown).

Effect of c-Met Inhibition on Cell Migration and Invasion

To test the hypothesis that c-Met function is required for IGF-I-mediated migration and invasion, c-Met was down-regulated with a ribozyme, and protein levels were measured. Previous reports with this same c-Met ribozyme have shown parallel decreases in mRNA on Northern blot with protein levels on Western blot (39). Total c-Met levels were measured at 24 and 48 hours, corresponding with the beginning and termination, respectively, of the cell migration assays.

The ad-c-Met ribozyme resulted in a 28% decrease in total c-Met protein levels at 24 hours compared with the control (ad-pU1; Fig. 3A). At 48 hours, the total c-Met level remained decreased (data not shown). Despite this relatively small decrease in overall expression, in previous studies, we have observed that a relatively small decrease in protein levels leads to a pronounced effect on kinase activity (43). Therefore, we determined the effect of the ribozyme on intrinsic c-Met kinase activity using an immune complex kinase assay. The ad-c-Met ribozyme decreased c-Met kinase activity by 63% compared with the control (ad-pU1; Fig. 3A). These data again showed that a modest reduction in c-Met expression levels leads to substantially reduced c-Met function.

The ad-c-Met ribozyme did not alter the level of total IGF-IR compared with control (ad-pU1; Fig. 3A). Similarly, ad-c-Met ribozyme did not alter IGF-IR phosphorylation compared with control (ad-pU1, data not shown). An MTT assay showed that the ad-c-Met ribozyme did not change cell survival relative to the ad-pU1 control (data not shown).

The L3.6pl cells infected with ad-pU1 (control) migrated in response to IGF-I, HGF, and IGF-I plus HGF (Fig. 3B) in a manner similar to that of the parental cells (Fig. 1), showing that adenoviral infection with the control plasmid (pU1) did not alter the migration response to these growth factors. In contrast, inhibition of c-Met with the ad-c-Met ribozyme led to a mean 95 ± 1% decrease in HGF-mediated migration (P < 0.0001) compared with ad-pU1-infected control cells (Fig. 3B). This was expected because HGF signals via the c-Met receptor. Interestingly, c-Met inhibition in the ad-c-Met ribozyme cells also led to a mean 96 ± 1% decrease in migration in the IGF-I-treated group (P < 0.0001) and a mean 91 ± 1% decrease in migration in the IGF-I/HGF-treated group (P < 0.005) compared with ad-pU1-infected control cells (Fig. 3B).

In addition, c-Met inhibition led to a mean 83 ± 9% decrease in cell migration (P = 0.0011) in the PBS-treated cells compared with the ad-pU1-infected cells treated with PBS (Fig. 3B).
Transwell invasion assays were done with cells infected with the ad-c-Met ribozyme or ad-pU1 to determine the role of c-Met function in IGF-I- and HGF-mediated cell invasion. As was observed in the migration assay, the ad-c-Met ribozyme–infected cells exhibited a mean 97% decrease in HGF-induced cell invasion (P < 0.0001) compared with ad-pU1-infected control cells treated with HGF (Fig. 3C). Inhibition of c-Met function also resulted in a mean 92% decrease in cell invasion in the IGF-I-treated group (P < 0.0001) and a mean 96% decrease in cell invasion in the IGF-I/HGF-treated group (P < 0.0001). Inhibition of c-Met function resulted in no significant change in cell invasion in the PBS-treated group. Thus, IGF-I and HGF seem to mediate cell migration and invasion via a c-Met-dependent pathway.

As an internal control, an MTT assay was done under the same conditions as the migration and invasion assays to ensure that cell proliferation was not affected by ad-pU1 or ad-c-Met ribozyme infection. There was no change in cell number in the ad-pU1-infected control cells in response to treatment with IGF-I, HGF, or IGF-I plus HGF compared with PBS (data not shown). The ad-c-Met ribozyme–infected cells exhibited a mean 18% decrease in cell number with PBS treatment (P < 0.05) and a mean 19% decrease in cell number with IGF-I plus HGF treatment (P < 0.05) compared with ad-pU1-infected cells (data not shown), but IGF-I treatment and HGF treatment did not affect cell numbers in ad-c-Met ribozyme–infected cells compared with ad-pU1-infected cells (data not shown). Thus, the substantial inhibition of cell migration and invasion achieved in the c-Met ribozyme–infected cells was not due to the cytotoxicity of ribozyme infection.

**Effect of IGF-I on Total c-Met and c-Met Phosphorylation**

To determine whether IGF-I increased total or phosphorylated c-Met protein levels, cells were incubated with PBS or IGF-I for 24 hours, and then cellular protein was harvested for determination of total and phosphorylated forms of c-Met by Western blotting. IGF-I treatment did not alter levels of total mature c-Met or phosphorylated c-Met (data not shown).

**Discussion**

Pancreatic adenocarcinomas are highly invasive malignancies that have a propensity to metastasize early. These tumors have been shown to express IGF-IR (11) and c-Met (12) at high levels relative to normal adjacent pancreatic tissue. Both IGF-IR (19–23) and c-Met (12, 18, 24–26) activation have been shown to induce tumor cell invasion and migration, which are critical events in tumor metastasis. However, until now, cooperation or cross-talk between these two tyrosine kinase receptors has not been shown in pancreatic carcinomas.

In this study, we showed that the combination of IGF-I plus HGF led to a greater than additive increase in the migration and invasion of L3.6pl human pancreatic carcinoma cells compared with IGF-I or HGF alone.
These findings suggest cooperation between the IGF-I/IGF-IR and HGF/c-Met pathways. In addition, we found that c-Met inhibition with a c-Met ribozyme nearly completely blocked HGF-mediated migration and invasion, as would be expected, but also nearly completely inhibited IGF-I-mediated migration and invasion. IGF-I stimulation of cells did not alter the total or phosphorylated forms of c-Met. Together, these data show that IGF-I and HGF cooperate to induce migration and invasion and that c-Met regulates IGF-I-mediated migration and invasion.

The c-Met ribozyme used in this study has been validated and published previously in two additional human cancer cell lines, and the degree of inhibition in total c-Met protein level (28% decrease in the present study) and the degree of inhibition in c-Met kinase activity (63% decrease in the present study) were similar in these two cell lines. In the human colon cancer cell line KM20, the c-Met ribozyme led to a 26–32% decrease in total c-Met protein level, which led to a 64% to 77% decrease in c-Met kinase activity (40). In another study with the human colon cancer cell line KM12, the c-Met ribozyme led to a 15% decrease in total c-Met protein level, which led to an 80% decrease in c-Met kinase activity (41). The similarity in the results achieved with the c-Met ribozyme in these three cell lines helps to validate this molecular tool.

This study is the first to show cooperation between IGF-IR and c-Met in a human pancreatic cancer cell line. Although studying individual growth factors or signaling molecules in isolation is necessary to define their specific cellular effects and the signaling pathways mediating these effects, that approach may not identify crucial interactions, cooperation, or cross-talk between signaling pathways. Given the complexity of growth factor signaling in pancreatic carcinoma cells and the multiple tyrosine kinase receptors that are simultaneously up-regulated in those cells, studies evaluating the effects of the interaction of multiple growth factors on cell behavior are essential if we are to attempt to duplicate in vitro conditions that occur in vivo.

Although cooperation between IGF-IR and c-Met signaling is the most likely explanation for our findings, an alternative explanation could be that c-Met function is critical for any migration, independent of IGF-I signaling. This hypothesis would not explain the greater than additive effect of IGF-I plus HGF on cell migration and invasion. Another hypothesis could be that the cooperation between IGF-I and HGF in cell migration and invasion is due to augmentation of downstream signaling pathways. However, this hypothesis could not explain the c-Met ribozyme data. Thus, our data showing the greater than additive effect of IGF-I plus HGF on cell migration and invasion and the inhibition of IGF-I-mediated migration and invasion by the c-Met ribozyme without inhibition of IGF-IR phosphorylation are best explained by IGF-IR and c-Met cooperation. The level of this cooperation seems to be downstream of the IGF-IR and c-Met receptors.

In conclusion, our data suggest that IGF-IR and c-Met are valid targets for pancreatic carcinoma therapy and warrant further investigation. Although there are several agents targeting the IGF-IR pathway in clinical trials, the finding that c-Met is a downstream mediator of IGF-IR-induced migration and invasion suggests that inhibitors of c-Met should also be investigated as a component of therapy for pancreatic cancer.

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References

c-Met-Mediated Invasion in Pancreatic Carcinoma


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