Pancreatic cancer is one of the most aggressive malignant diseases. We recently reported that N-cadherin plays a key role in tumor progression and metastasis in pancreatic cancer. In addition, recent studies have indicated that synthetic short cyclic peptides containing the sequence, His-Ala-Val (HAV), which is found in the first extracellular (EC1) domains of all classical cadherins, inhibit cadherin-based cell-cell interactions and was used as a control peptide (Williams E et al., J Biol Chem 2000;275:4007-12). The cyclic peptides used in this study, ADH-11 (N-Ac-CHGVDC-NH2) and ADH-1 (N-Ac-CHAVC-NH2) were kindly provided by Adherex Technologies Inc. ADH-11 had no effect on N-cadherin mediated cell-cell interactions and was used as a control peptide.

Experimental Design: The effect of ADH-1 on N-cadherin-mediated cell scattering and migration in response to collagen I was examined using pancreatic cancer cells (BxPC-3 and Capan-1). We also examined the influence of ADH-1 on cell proliferation and apoptosis. Furthermore, in vivo animal studies were performed using orthotopic injection of N-cadherin over-expressing BxPC-3 cells with or without ADH-1 treatment.

Results: BxPC-3 and Capan-1 cells showed increased expression of N-cadherin in response to collagen I. This increase in N-cadherin promoted cell scattering and migration. In contrast, ADH-1 prevented these changes, which did not in up-regulate expression of N-cadherin. TUNEL assays showed that ADH-1 induced apoptosis in a concentration-dependent manner and N-cadherin dependent manner. We recently reported that pancreatic cancer cells knocked down for N-cadherin formed significantly smaller tumors as compared to N-cadherin over-expressing cells using an orthotopic mouse model for pancreatic cancer. Histological examination demonstrated micro-metastases in the lungs of mice bearing tumors comprised of N-cadherin knockdown cells. In agreement with these data, blocking N-cadherin function by ADH-1 treatment resulted in significant reductions in tumor growth and lung metastasis in a mouse model for pancreatic cancer.

Conclusions: The N-cadherin antagonist, ADH-1 has significant anti-tumor activity against N-cadherin-expressing cells using in vitro assays and in an orthotopic mouse model for pancreatic cancer, raising the possibility that N-cadherin antagonists have therapeutic potential for the treatment of pancreatic cancer in humans.

Introduction


Blaesdl et al. reported that synthetic peptides containing the sequence, His-Ala-Val (HAV), which is found in the first extracellular (EC1) domain of all classical cadherins, inhibited cadherin-based cell-cell interactions (Dev Biol 1998;197:227-30). In addition, recent studies have indicated that short cyclic HAV peptides can inhibit N-cadherin function (Williams E et al., J Biol Chem 2000;275:4007-12).

We recently reported that pancreatic cancer cells undergo cell scattering and N-cadherin up-regulation in response to type I collagen, but not to other matrices, and that up-regulation of N-cadherin is necessary for collagen I-induced cell motility (Shintani et al., Cancer Res 2006;66:11745-53). We also showed that pancreatic cancer cells knocked down for N-cadherin formed significantly smaller tumors as compared to N-cadherin over-expressing cells using an orthotopic mouse model for pancreatic cancer. Histological examination demonstrated micro-metastases in the lungs of mice bearing tumors comprised of N-cadherin knockdown cells. In agreement with these data, blocking N-cadherin function by ADH-1 treatment resulted in significant reductions in tumor growth and lung metastasis in a mouse model for pancreatic cancer.

Conclusions: The N-cadherin antagonist, ADH-1 has significant anti-tumor activity against N-cadherin-expressing cells using in vitro assays and in an orthotopic mouse model for pancreatic cancer, raising the possibility that N-cadherin antagonists have therapeutic potential for the treatment of pancreatic cancer in humans.