

Pancreatic Cancer

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Gene Expression Profiling Differentiates Drug-Sensitive and Drug-Resistant Pancreatic Cancer Cell Lines

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Background: Pancreatic cancer is the fourth leading cause of cancer death in the United States. Unfortunately, there remains no effective therapy available to treat this aggressive tumor. Although most chemotherapy regimens utilize gemcitabine as the clinical standard of care for pancreatic cancer, patients generally have limited response to this therapy. Combination therapy and targeted therapies have also been quite disappointing overall. Thus, a better global understanding of the molecular mechanisms underlying drug resistance in pancreatic cancer may lead to the development of more effective therapeutic interventions.

Methods: Responses of human pancreatic cancer cell lines (BxPC3, CFPAC, L3.6pl, SU 86.86, AsPC-1, Hs 766T, MIA PaCa-2, Mpanc96, PANC-1 and HPDE) to four conventional chemotherapeutic agents (gemcitabine, 5-fluorouracil, cisplatin, and paclitaxel) were assessed by cell viability (MTS assay) and apoptosis (FACS analysis) assays. Gene expression profiling was analyzed by Illumina microarray and was confirmed by Q-RT-PCR and immunohistochemistry.

Results: Five cell lines (HPDE, L3.6pl, BxPC3, CFPAC-1, SU 86.86) were relatively sensitive, whereas five (PANC-1, Hs 766T, AsPC-1, MIA PaCa-2, Mpanc96) were highly resistant to all four drugs. Gene expression profiling revealed that the drug-sensitive and -resistant cells differed in features of “epithelial-mesenchymal transition”

(EMT), including cell adhesion, polarity, junction, and motility genes. Interestingly, inverse correlations of E-cadherin and its transcriptional suppressor, Zeb-1; and Zeb-1 and its mRNA suppressor, mir-200c, were observed in pancreatic tumor and cell lines. Silencing of Zeb-1 reversed EMT by restoring epithelial gene expression and drug sensitivity, thus implicating Zeb-1 and EMT in global drug resistance in pancreatic cancer.

Conclusions: This study revealed a distinct gene expression pattern common to drug-resistant pancreatic cancer cells. Resistance was not restricted to a single agent but was generalized to a wide spectrum of cytotoxic agents. Gene profiling indicated a shared profile among resistant cells. Genes identified in this panel of cells may be useful for predicting resistance and may be targets for improved therapy.