P65. PREDICTION OF METASTASES AND LOCAL TUMOR INVASION IN PANCREATIC CANCER USING AN ORTHOTOPIC SCID MOUSE MODEL

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Background: Gene expression profiling in pancreatic cancer is complicated by the high amount of RNAses in human tissue and suitable models. In order to reflect early metastasizing, models should be constructed with respect to the anatomical environment. Using the orthotopic pancreatic tumor SCID mouse model these interactions are taken into account. In order to identify genes associated with local tumor invasion and metastases in ductal pancreatic cancer we investigated pancreatic tumor cell lines derived from an orthotopic pancreatic tumor model in SCID mice. Differential gene expression was performed based on cDNA microarray technique.
Methods: Human MiaPaca cell lines were orthotopically implanted in SCID mice ($n = 18$). Transcriptional profiling (Affymetrix, HGU133) was performed with tissue derived from the primary tumor, duodenal tumor invasion frontier, and liver metastases. Differentially expressed genes were identified after statistical analysis (ANOVA) and validated with external data bases (NCBI: PubMed, LokuslLink, Unigene, Swissprot, Geneontology).
Results: Of 22283 genes investigated, 1066 were high significantly altered ($p < 10^{-6}$). With respect to the primary tumor, in liver metastases 196 genes were differentially expressed, whereas in the duodenal tumor invasion frontier 964 genes were altered. Comparing current data bases we established a panel of 14 genes associated with liver metastases and local invasion for functional validation. These genes can be assigned to apoptosis (e.g. BNIP3L, GADD45A), angiogenesis (VEGF), or cell migration and -adhesion (SERPINE1).
Conclusion: The SCID mouse model is able to simulate the human metastasizing cascade in vivo and facilitate gene expression analyses. Using transcriptional profiling in the SCID mouse model marker genes for local invasion and liver metastases can be identified. These marker genes are associated with apoptosis, angiogenesis, and cell interactions.

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P66. THE THROMBIN RECEPTOR PAR-1 PLAYS AN IMPORTANT ROLE IN PANCREATIC CANCER CELL INVASIVENESS IN VITRO

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Background: Thrombosis and activation of coagulation are frequently observed in cancer patients. This phenomenon is reflected in the excess production of thrombin, which is thought to play an important role in the progression of different solid tumors. Cellular effects of thrombin are mediated by the thrombin receptor PAR-1, a member of the G-protein coupled receptor family. Aim of this study was to investigate the role of PAR-1 on pancreatic cancer cell invasion.
Material and Methods: The human pancreatic cancer cell line MIA PaCa-2, which expresses high levels of PAR-1, was transfected with an antisense construct against PAR-1. The expression level of PAR-1 after transfection was determined by RT-PCR and Western blot analysis. For invasion assays the respective transfected, control transfected (sense and mock) and untransfected cells were stimulated with thrombin (1.0 U/ml) and subjected to a standardized Matrigel invasion assay. After 24 h the number of invasive cells were counted.
Results: Antisense transfection resulted in 80% downregulation of PAR-1 expression compared to parental MIA PaCa-2. In the Matrigel invasion assay the number of invasive cells was significantly reduced for the antisense transfected cells. The control transfected cells showed no change of invasiveness compared to untransfected MIA PaCa-2.
Conclusion: The expression of the thrombin receptor PAR-1 was successfully reduced in pancreatic cancer cells by antisense transfection. Downregulation of the thrombin receptor lead to significantly reduced invasiveness in vitro. These results emphasize the crucial role of PAR-1 in pancreatic cancer progression in vitro. In vivo assays to confirm the impact of PAR-1 expression on pancreatic cancer cell invasiveness are prospected.

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P67. PRETHERAPEUTICAL GENE EXPRESSION PROFILING FOR RESPONSE PREDICTION OF RECTAL ADENOCARCINOMAS TO PREOPERATIVE CHEMORADIOTHERAPY AND ITS IMPACT ON DISEASE FREE SURVIVAL

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Background: There is a wide spectrum of tumor responsiveness of rectal adenocarcinomas to preoperative chemoradiotherapy (CT/RT) ranging from complete response to resistance. We therefore investigated whether gene expression profiling can assist in stratifying patients into responders or non-responders. Furthermore, we evaluated whether distinct gene expression signatures can be used for individualized prognostication (disease free survival).
Methods: Pretherapeutic biopsies from 30 locally advanced rectal carcinomas were analyzed using microarrays. Class comparison was used to identify a set of genes that were differentially expressed between responders and non-responders (as measured by T-level down-sizing). Leave-one-out cross-validation (LOOCV) was performed to explore the predictive value of the identified gene-set.
Results: Responders and non-responders showed significantly different expression levels for 54 genes ($p < 0.001$). When we