Examination of apoptosis signaling in pancreatic cancer by computational signal transduction analysis.

BACKGROUND: Pancreatic ductal adenocarcinoma (PDAC) remains an important cause of cancer death. Changes in apoptosis signaling in pancreatic cancer result in chemotherapy resistance and aggressive growth and metastasizing. The aim of this study was to characterize the apoptosis pathway in pancreatic cancer computationally by evaluation of experimental data from high-throughput technologies and public data bases. Therefore, gene expression analysis of microdissected pancreatic tumor tissue was implemented in a model of the apoptosis pathway obtained by computational protein interaction prediction.

METHODOLOGY/PRINCIPAL FINDINGS: Apoptosis pathway related genes were assembled from electronic databases. To assess expression of these genes we constructed a virtual subarray from a whole genome analysis from microdissected native tumor tissue. To obtain a model of the apoptosis pathway, interactions of members of the apoptosis pathway were analysed using public databases and computational prediction of protein interactions. Gene expression data were implemented in the apoptosis pathway model. 19 genes were found differentially expressed and 12 genes had an already known pathophysiological role in PDAC, such as Survivin/BIRC5, BNIP3 and...
TNF-R1. Furthermore we validated differential expression of IL1R2 and Livin/BIRC7 by RT-PCR and immunohistochemistry. Implementation of the gene expression data in the apoptosis pathway map suggested two higher level defects of the pathway at the level of cell death receptors and within the intrinsic signaling cascade consistent with references on apoptosis in PDAC. Protein interaction prediction further showed possible new interactions between the single pathway members, which demonstrate the complexity of the apoptosis pathway. CONCLUSIONS/SIGNIFICANCE: Our data shows that by computational evaluation of public accessible data an acceptable virtual image of the apoptosis pathway might be given. By this approach we could identify two higher level defects of the apoptosis pathway in PDAC. We could further for the first time identify IL1R2 as possible candidate gene in PDAC.