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Assessment of genes associated with immune activation and regulation in pancreatic cancer patients

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Pancreatic adenocarcinoma is among the most fatal of gastrointestinal cancers. Recent *in vitro* studies showed that tumors are able to develop several escape mechanisms. We hypothesized that regulatory T cells (Treg) may impair anti-tumor immune responses. Therefore, we investigated the role of immune-mediated pathways in invasive pancreatic cancer.

Blood and tumor samples were analyzed in 14 patients undergoing surgery for pancreatic adenocarcinoma (UICC stages II to IV) by ELISA, immunohistology, and real-time RT-PCR techniques. The expression, distribution, and protein products of the following gene classes were analyzed:Treg (CD4, CD25, CD8, IDO, Foxp3), co-stimulatory molecules (CD28, CTLA-4), transcription factors (GITR, GATA-3), apoptotic markers (Bcl-2, Fas, FasL), cytokines (IFN-γ, IL-6/10), tumor suppressors (p53, APC), and tumor marker (CEA).

Immunohistogical/-fluorescence doublestaining corresponded with the PCR results for the various markers (CD4+CD25+, CD8+CD28+, Bcl-2, Fas/FasL, p53/CD4+, CEA/CD4+, APC). Using hierarchical clustering methods the comparison of all tumor tissues revealed two samples with a highly different gene expression pattern. The dissimilarity was associated with the UICC stage of the patients. Compared to UICC III or IV, stage II showed a significantly lower expression of most genes (14 out of 19). The other characteristic difference in the gene expression pattern of the individual sample was due to the localization of the analyzed tissue within the tumor. Samples from the tumor center showed a markedly lower expression of the immune-response related genes than samples from the tumor border line. Gene expression related to immune activation and regulation was low (CD69<Foxp3 & CTLA-4<CD28 & IFN-γ & IL-10 & CD4<IDO & CD25 & GATA-3<Fas & IL-6) in all samples obtained from the tumor center. The anti-apoptotic genes Bcl-2 and GITR showed a higher expression than the pro-apoptotic genes Fas and FasL. The highest expression was measured for APC>CEA>Bcl-2>CD8. IFN-γ & CTLA4 & CD28; CD4 & IL-10 & Foxp3 & CD25; and Bcl-2 & APC were clustered together analyzing the patterns of gene expression among the different samples.

Invasive pancreatic carcinomas show relatively low levels in expression of genes associated with immune activation and regulation. This might indicate insufficient anti-tumor immune responses against the tumor. In addition, gene expression profiles differ significantly between samples obtained from the tumor center versus the tumor border line.