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Searching for predictive molecular markers for chemoradioimmunotherapy (with interferon-α) and chemotherapy (with 5-fluorouracil) of pancreatic cancer

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"Infiltrating ductal adenocarcinoma of the pancreas" is a horrifying diagnosis for any patient with a very poor prognosis, a 5-year survival rate of less than 5% (all stages combined) and a median survival of 3.5 months without resection (US). Due to early formation of metastasis and late diagnosis, palliative chemotherapy is the only option for most of the patients (~50-60%). Curative surgical resection and subsequent adjuvant chemotherapy is feasible in early diagnosed patients (~20%), resulting in a median survival of around 20 months. Facing these challenging statistics and the personal tragedy of such a diagnosis, it is crucial to find alternative treatment options. The CapRI study, a recent multicenter clinical trial on intensified adjuvant chemoradioimmunotherapy (CRI) with IFN-α, failed to significantly increase survival compared to standard chemotherapy alone (5-FU). Nonetheless, it presented the highest mOS ever reported for pancreatic cancer patients in a randomized trial. Furthermore, it indicated increased response in high risk patients and a significantly reduced risk of local tumor recurrence. As the importance of individualized therapy finds its way more and more into the awareness of scientist and medical doctors, the main aim of this thesis was to identify and validate predictive molecular markers capable of a preselection of patients suitable for CRI with IFN-α.

Therefore, responder and non-responder patients to CRI were defined upon their survival rate. RNA from frozen tumor tissues of both groups was isolated and used for whole genome expression analysis with Illumina technology. The 12 most promising candidates to be differentially expressed and of predictive value were validated via qPCR. Bio-statistical analysis utilizing the Cox PH model was applied to identify significant predictors of overall survival (OS) and disease-free survival (DFS). Additionally, the most promising gene candidates were validated via qPCR expression analysis upon pancreatic cancer cell lines compared to normal pancreatic tissue cell lines.

Highly significant predictors for the OS of the patients appeared to be GAGE5 (p-value = 0.0099), as well as MAP3K2 (p-value = 0.055) and RTEL1 (p-value = 0.06). 3 genes were detected to be highly significant predictors for the DFS: GAGE5 (p-value = 0.0088), MAP3K2 (p-value = 0.02444) and TCEA1 (p-value = 0.0304). RTEL1 and MAP3K2 are significantly upregulated in pancreatic cancer cell lines (p-value: ≤ 0.05). In contrast, OR4M2 is downregulated in pancreatic cancer cell lines (p-value: ≤ 0.05). GAGE5 and RAET1L are exclusively expressed in pancreatic cancer cell lines.

Expression level of GAGE5, MAP3K2 and RTEL1 has been found to be predictive for the OS, and GAGE5, MAP3K2 and TCEA1 for the DFS of patients undergoing chemoradioimmunotherapy. Their predictive value should be further validated in a prospective clinical trial. Previous preclinical experimentation could provide insights concerning the molecular mechanisms behind there explanatory power and link the prolonged survival of responder patients to an effect of IFN-α. These markers are of great value regarding individualized therapy and the application of immunotherapy in patients with pancreatic cancer.