Identification of tissue biomarkers of prognostic significance in pancreatic cancer

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ABSTRACT

Background: Pancreatic cancer is the third leading cause of cancer-related mortality. Lack of early detection strategy and therapeutic resistance are main contributors of the poor prognosis. Unfortunately, there are few biomarkers available for the prognosis of pancreatic cancer in routine clinical use.

Aim: To identify and validate novel biomarkers for the prognosis of pancreatic cancer.

Method: Mass spectrometry-based proteomic approach was applied to formalin-fixed paraffin-embedded specimens from 9 patients with pancreatic cancer with short survival and 10 patients with long survival undergoing surgical resection. The dysregulated biomarkers were further verified by
targeted proteomics, parallel reaction monitoring. Finally, we evaluated prognostic candidates, CLCA1 and galectin 4, by tissue microarrays and immunohistochemistry in 140 patients with pancreatic cancer who underwent surgical resection. Bioinformatics analysis was exploited to assess pathways and networks linked to the prognosis. Kaplan-Meier and Cox proportional hazards modeling were used to explore the association between biomarkers and survival.

**Preliminary results:** A total of 24 and 147 proteins were significantly upregulated in patients with short survival and long survival, respectively. Bioinformatics analyses linked proteins representing “activated stroma factors” and “basal tumor factors” to poor prognosis and highlighted TCF1 and CTNNB1 as possible upstream regulators. By targeted proteomics, seven proteins were verified to be upregulated in patients with short survival (MMP9, CLIC3, MMP8, PRTN3, P4HA2, THBS1 and FN1), while 18 proteins were upregulated in patients with long survival, including EPCAM, galectin 4, VIL1, CLCA1 and TPPP3. By immunohistochemical validation, low CLCA1 expression correlated significantly with shorter disease-free survival (11.9 vs 17.5 months, adjusted HR 0.54, P=0.005). Furthermore, galectin 4 expression was significantly correlated with disease recurrence within 1 year of surgery (adjusted HR 0.49, P=0.027). There was also a significant association between galectin 4 and overall survival at 1 year (adjusted HR 0.48, P=0.047) and at 3 years (adjusted HR 0.55, P=0.025).

**Conclusion:** Twenty-five tissue biomarker candidates for pancreatic cancer prognosis have been identified and verified by proteomics approach. Low CLCA1 expression is an independent factor of poor disease-free survival in pancreatic cancer. Furthermore, galectin 4 expression is a novel biomarker for early recurrence and mortality after surgical resection for pancreatic cancer.

**Papers:**

