MALDI imaging mass spectrometry for in situ proteomic analysis of preneoplastic lesions in pancreatic cancer.

The identification of new biomarkers for preneoplastic pancreatic lesions (PanINs, IPMNs) and early pancreatic ductal adenocarcinoma (PDAC) is crucial due to the disease's high mortality rate upon late detection. To address this task, we used the novel technique of matrix-assisted laser desorption/ionization (MALDI) imaging mass spectrometry (IMS) on genetically engineered mouse models (GEM) of pancreatic cancer. Various GEM were analyzed with MALDI IMS to investigate the peptide/protein-expression pattern of precursor lesions in comparison to normal pancreas and PDAC with cellular resolution. Statistical analysis revealed several discriminative m/z-species between normal and diseased tissue. Intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasm (IPMN) could be distinguished from normal pancreatic tissue and PDAC by 26 significant m/z-species. Among these m/z-species, we identified Albumin and Thymosin-beta 4 by liquid chromatography and tandem mass spectrometry (LC-MS/MS), which were further validated by immunohistochemistry, western blot, quantitative RT-PCR and ELISA in both murine and human tissue. Thymosin-beta 4 was found significantly increased in sera of mice with PanIN lesions. Upregulated
PanIN expression of Albumin was accompanied by increased expression of liver-restricted genes suggesting a hepatic transdifferentiation program of preneoplastic cells. In conclusion we show that GEM of endogenous PDAC are a suitable model system for MALDI-IMS and subsequent LC-MS/MS analysis, allowing in situ analysis of small precursor lesions and identification of differentially expressed peptides and proteins.