Novel prognostic markers revealed by a proteomic approach separating benign from malignant insulinomas.

The prognosis of pancreatic neuroendocrine tumors is related to size, histology and proliferation rate. However, this stratification needs to be refined further. We conducted a proteome study on insulinomas, a well-defined pancreatic neuroendocrine tumor entity, in order to identify proteins that can be used as biomarkers for malignancy. Based on a long follow-up, insulinomas were divided into those with metastases (malignant) and those without (benign). Microdissected cells from six benign and six malignant insulinomas were subjected to a procedure combining fluorescence dye saturation labeling with high-resolution two-dimensional gel electrophoresis. Differentially expressed proteins were identified using nano liquid chromatography-electrospray ionization/multi-stage mass spectrometry and validated by immunohistochemistry on tissue microarrays containing 62 insulinomas. Sixteen differentially regulated proteins were identified among 3000 protein spots. Immunohistochemical validation revealed that aldehyde dehydrogenase 1A1 and voltage-dependent anion-selective channel protein 1 showed significantly stronger expression in malignant insulinomas than in benign insulinomas, whereas tumor protein
D52 (TPD52) binding protein was expressed less strongly in malignant insulinomas than in benign insulinomas. Using multivariate analysis, low TPD52 expression was identified as a strong independent prognostic factor for both recurrence-free and overall disease-related survival.