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Proteome Profiling of Pancreatic Ductal Adenocarcinoma and Specific Detection of Kallikrein Proteases -6 and -10 by Targeted and Explorative Mass Spectrometry

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Pancreatic ductal adenocarcinoma (PDAC) is one of the deadliest malignancies in the world with most patients representing themselves in a metastatic stage. Thus, PDAC urgently needs new therapeutic approaches and the identification of novel biomarkers which enable early diagnosis. In PDAC, two members of the human tissue kallikrein family (KLK), KLK6 and KLK10, were shown to be significantly upregulated and are hence assumed to play critical roles in its malignant progression. However, little is known so far about their contribution to pathophysiology of pancreatic cancer. Therefore, we performed targeted and explorative mass spectrometry (MS) to qualitatively and quantitatively investigate KLK proteins in conditioned pancreatic cancer cell media as well as PDAC formalin-fixed paraffin-embedded (FFPE) tissues and also performed an explorative proteome profiling of PDAC to better understand the disease-related proteome biology. Initially, a robust and reproducible sample preparation workflow was established for the enrichment and detection of KLKs in conditioned pancreatic cancer cell media and PDAC FFPE tissue. The targeted approach demonstrated cell line specific secretion of KLK6 and KLK10. Moreover, we found significantly upregulated KLK6 and KLK10 protein levels in malignant tissues of PDAC and ampullary cancer compared to controls. Both targeted and explorative analysis further highlight the “Warburg effect” in PDAC, with a significant upregulation of glycolytic proteins and downregulation of the mitochondrial energy metabolism. In addition, PDAC showed a significant overexpression of proteins involved in cell adhesion, which stands in contrast to the epithelial-to-mesenchymal transition (EMT) theory and suggests a collective cell migration rather than single cell dissemination. In summary, our data of the targeted analyses suggest that KLK6 and KLK10 are an integral part of PDAC tumor biology and may be potential biomarkers, while the explorative analysis revealed interesting up- and downregulated proteins within the different conditions, all of which require further validation in larger patient cohorts.