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Uncovering Filamin A as an Exosomal Biomarker in PanNET Through Integrative Tissue Proteomics

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BACKGROUND

Pancreatic neuroendocrine tumors (PanNETs) are rare neoplasms, with increasing incidence and poor survival rate. The disease is diagnosed at advanced stages due to the lack of diagnostic sensitivity and specificity of the biomarkers, inaccessible and expensive nature of the imaging techniques available. Proteomics plays a significant role in cancer research and aids in the discovery of biomarkers. This study aimed to identify potential PanNET biomarkers through tissue proteomics and explore their relevance in circulating exosomes.

METHODS

A comparative label-free quantitative proteomic analysis was conducted on 6 PanNET tissue samples (3 Grade I and 3 Grade II) and 6 control pancreatic tissues (3 normal healthy and 3 adjacent non-tumor) after getting ethical approval from the institute's ethical committee (IECPG-452/25.08.2). Multiple group-wise comparisons were performed to identify differentially expressed proteins. Potential biomarker proteins were validated using molecular assays. Functional associations were analyzed via STRING-based pathway and protein interaction analysis. Small extracellular vesicles (sEVs) were isolated from the plasma of PanNET patients and healthy controls to evaluate the exosomal enrichment of candidate proteins.

RESULTS

The proteomic analysis by LC-MS revealed a total of 78.4% identified proteins that were uniquely expressed in PanNETs, with 30 proteins significantly dysregulated between PanNETs and normal healthy controls with $p < 0.05$, fold change >2. Among these, 11 proteins were found to be upregulated and 19 were downregulated in abundance value in patients with respect to controls. Functional analysis of the dysregulated proteins with STING PPI-network revealed four pancreas-specific proteins (DCN, FlnA, COL1A2, and CALR) that showed strong associations with cancer-related pathways like antigen processing and presentation and proteoglycans in cancers. Preliminary validation using western blot and immunohistochemistry highlighted Filamin A (FlnA) as a significantly overexpressed protein in PanNET tissues as compared to healthy controls. Additionally, STRING analysis indicated FlnA's involvement in exosome-related networks. Further analysis of plasma-derived small extracellular vesicles (sEVs)/exosomes demonstrated significant upregulation of FlnA in PanNET patients compared to healthy controls, confirming its presence and enrichment in circulating exosomes.

CONCLUSIONS

This integrative approach, spanning tissue proteomics to exosomal profiling, identifies Filamin A as a promising biomarker candidate in PanNET. Its consistent overexpression in both tumor tissues and plasma-derived exosomes underscores its potential as circulating biomarker for non-invasive diagnostic applications.

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