B-3

Investigating the Role of Oncometabolites in von Hippel Lindau disease-related Pancreatic Neuroendocrine Neoplasms

Yuval Yossef[1], Liav Sela Peremen[1], Reut Halperin[1,2], Gil Goldinger[1,3], Naama Peshes Yaloz[2], Amit Tirosh[1,2].

[1]Tel Aviv University, Tel Aviv, Israel; [2]ENTIRE Center, Sheba Medical Center, Tel Aviv, Israel; [3]Institute of Pathology, Sheba Medical Center, Tel Aviv, Israel.

BACKGROUND

Von Hippel Lindau (VHL)-related pancreatic neuroendocrine tumors (PNETs) are distinct from sporadic PNETs (sPNETs), exhibiting unique genetic and clinical traits. Pseudohypoxia, resulting from VHL protein deficiency, leads to robust metabolic shift. Yet, its effect on vPNET neoplastic drive remains elusive.

METHODS

Metabolomics analysis was performed on vPNETs and sporadic PNET (sPNET) samples through LC-MS. Data were processed using MetaboAnalyst. Single nucleus RNA sequencing (snRNA-seq) analysis was conducted on eight samples (five sPNETs and three vPNETs), including clustering and annotation via the Seurat package, copy number alteration analysis, pathway enrichment analyses, cell trajectory, and pseudo-time analysis. Immunofluorescence staining was carried out on tumor samples using synaptophysin and ADORA2B antibodies.

RESULTS

In unbiased metabolomic profiling of vPNETs (n=3) and sPNETs (n=5), we found elevated adenosine monophosphate (AMP) levels in vPNETs that were redetected in a validation cohort. Through snRNA-seq, we identified malignant NE cells in each sample. Copy number alteration analysis revealed distinct changes in vPNET, with copy number losses in chromosomes 4 and 5, while sPNET showed gains in chromosomes 4, 5, 17, 19, and 20. Transcriptome-based pathway analysis of malignant cells demonstrated enrichment of hypoxia, glycolysis, apoptosis, and the PI3K-AKT-MTOR pathways in vPNET vs. sPNET. Pseudo-time analysis showed the origin and progression of malignant cells from non-malignant neuroendocrine cells. In our multi-omics analysis, combining metabolomics with snRNA-seq data, we found that purine metabolism was enriched in the top 50 variance metabolites corresponding to hypoxia-related genes. Immunofluorescence studies demonstrated a weak but positive expression of the adenosine 2B receptor expression on neuroendocrine cells.

CONCLUSIONS

We revealed the possible involvement of the adenosine pathway in the pro-tumoral drive of vPNET and characterized distinct cell types and genetic alterations between vPNETs and sPNETs. Our findings shed light on metabolic and cellular disparities between these tumor subtypes, offering insights for targeted therapeutic strategies.

ABSTRACT ID 28541