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Validation of Adversity-Linked Genes in Pancreatic Neuroendocrine Tumors

Mourad Bendjennat[1], Rachael Guenter[1], Brendon Herring[1], Elquis Castillo II[1], Stuart Phipps[1], Theo Hines[1], Isra Elhussin[2], Doug Welsch[3], Changde Cheng[3], Dai Chen[3], Upender Manne[4], Herbert Chen[1], Clayton Yates[2], Smita Bhatia[3], John Bart Rose[1], Andrea Gillis[1] (presenting, corresponding author).

[1]Department of Surgery, University of Alabama at Birmingham, USA; [2]Department of Pathology, Johns Hopkins School of Medicine, USA; [3]Department of Pediatrics, University of Alabama at Birmingham, USA; [4]Department of Pathology, University of Alabama at Birmingham, USA.

BACKGROUND

Health outcome differences exist among patients with pancreatic neuroendocrine tumors (pNET), particularly among those experiencing adverse social determinants of health (SDOH). These groups experience worse overall survival compared to their peers. Our team has previously reported significant intratumoral transcriptomic alterations linked to neighborhood adversity. This study aims to validate the expression of these novel transcriptomic changes in established pNET cell lines versus normal controls for future translational studies.

METHODS

We selected the top 20 differentially expressed genes (DEGs) from our prior transcriptomic analysis based on biological pathways' clinical relevance (malignancy, inflammation, and metabolism). We then evaluated the modulation of expression levels of these DEGs in pNET cell lines (BON-1 and/or QGP-1) compared to normal HPNE cells (hTERT-immortalized normal pancreatic) using western blotting and qPCR for protein and mRNA quantifications, respectively. We reviewed patients who underwent surgical resection for grade 1-2 pNETs at our institution (2006-2022) and created Tissue Microarrays (TMAs) from those patients. Qualitative immunofluorescence analysis was also performed on selected patients' tissue sections to confirm the colocalization of our DEGs with pNET markers: Chromogranin A and Synaptophysin.

RESULTS

We validated the enhanced expression of our top SDOH-associated pNET DEGs including: WFS1, MAX, cGAS, FAAH, SIRT6, SIGLEC8, and FBOX6, among others. Comparative immunoblotting of our target genes in HPNE versus BON-1 and QGP-1 showed altered expression levels in both types of pNET cell lines with several target genes being highly expressed similarly to known pNET markers, Chromogranin A and SSTR2. In parallel, qPCR assessments using BON-1 cells revealed that our DEGs were overexpressed from ~5 to ~400 fold over HPNE relative expression. As a reference, SSTR2 and Chromogranin A increased ~5 and ~300 fold in BON-1 versus HPNE cells, respectively. Finally, our patients' TMAs demonstrated co-localization of DEGs with pNET markers, Chromogranin A and Synaptophysin confirming intratumoral expression.

CONCLUSIONS

Our novel adversity associated genes have been validated experimentally with protein and mRNA expression levels in established pNET cell lines. Future directions will focus on exploring the role of these genes in driving more aggressive disease.

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