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RNA-sequencing Identifies Unique Molecular Features of Duodenal Neuroendocrine Tumors

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BACKGROUND: Although duodenal neuroendocrine tumors (DNETs) derive embryologically from the foregut, whether they transcriptionally resemble midgut NETs remains unknown. This study compared gene expression of NETs of the duodenum, foregut (pancreatic NETs; PNETs), and midgut (jejunoileal NETs; SBNETs).

METHODS: RNA-sequencing was performed on primary DNETs (n = 16), PNETs (n = 41), SBNETs (n = 37), and respective normal tissue. Biologically significant genes were identified by filtering for differentially expressed genes (DEGs) with an adjusted p-value of <0.01 and log2(fold change) ≤-2 or ≥2. Ingenuity Pathway Analysis (IPA) identified enriched pathways. Gene expression changes were plotted by principal component analysis (PCA), and median pairwise distance (MPD) compared differences between tumor type.

RESULTS: DNETs had 681 DEGs compared to normal tissue, with upregulation of PNET transcription factors ISL1 and PAX6. DNETs, PNETs, and SBNETs had 355 common differentially-expressed-versus-normal genes, including CGHA, CHGB, SYP, NEUROD1, TPH1, and WNT4. Enriched pathways included those involved in synaptogenesis, CREB signaling in neurons, and insulin secretion. 170 genes were specific to DNETs, with upregulation of glycoprotein VI and cAMP-mediated signaling pathways.Overall DNET gene expression was not more similar to PNETs or SBNETs (MPD 98.5 vs 91.7, p = 0.3). DNET expression was more similar to PNET expression in genes related to GABA receptor signaling (MPD 5.3 vs. 3.6, P = 0.001), but more similar to SBNETs in pathways associated with melatonin degradation, FXR/RXR activation, and SPINK1-associated pancreatic cancer.

CONCLUSION: Compared to normal tissue, DNETs have upregulation of PNET transcription factors ISL1 and PAX6. Although NETs from several sites share common differentially expressed genes, DNETs have distinct gene expression and are not more similar to either PNETs or SBNETs.

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Median pairwise distances between NETs from the duodenum, pancreas, and small bowel

Genes/Pathway	DNET vs PNET	DNET vs SBNET	P
Overall gene expression	98.51	91.7	0.262
PNET vs. SBNET top 1000 differentially expressed genes	25.89	27.12	0.474
CREB Signaling in Neurons (PNET vs. normal canonical pathway)	6.92	7.47	0.181
GABA Receptor Signaling (PNET vs. normal canonical pathway)	3.61	5.25	**0.001**
Synaptogenesis Signaling Pathway (PNET vs. normal canonical pathway)	4.87	4.45	0.277
Superpathway of Melatonin Degradation (SBNET vs. normal canonical pathway)	4.09	3.05	**0.001**
Melatonin Degradation I (SBNET vs. normal canonical pathway)	3.37	2.53	**0.002**
FXR/RXR Activation (PNET vs SBNET canonical pathway)	5.02	4.09	**0.042**
SPINK1 Pancreatic Cancer Pathway(PNET vs SBNET canonical pathway)	5.53	3.45	**0.001**