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Comparative gene expression and pathway analysis of neuroendocrine neoplasms in relation to clinical outcomes and tumor location

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BACKGROUND

Neuroendocrine malignancies are heterogeneous cancers with varied clinical outcomes. The molecular landscape driving this heterogeneity has not yet been fully characterized. We aimed to investigate the gene expression profiles of neuroendocrine neoplasms, in relationship to baseline clinicopathological features and clinical outcomes, to elucidate underlying biology and potential therapeutic targets.

METHODS

Patients with neuroendocrine tumors (NETs) and neuroendocrine carcinomas (NECs) treated at the Cleveland Clinic (2000-2022) with molecular profiling (N= 79) were identified. Quantified gene expression profiles were retrospectively retrieved from Tempus or Caris. Clinicopathological characteristics were obtained from the electronic health record. Statistical analyses were performed using R v.4.0.5 and R package Limma was used to identify differential gene expression. Tempus and Caris data were analyzed separately. Pathway analysis using gene set collections from the molecular signatures database (MSigDB) was performed by gene set enrichment analysis.

RESULTS

The cohort consisted of 41 patients with NECs and 38 NETs. Among NETs, 14 (37%) had Ki67>20%. The most common primary sites for NETs were small bowel (n=19, 50%) and pancreas (n=8, 21%), while for NECs colorectal (n=9, 23%) and bladder/prostate (n=9, 23%). Among NETs, *ARX*, *IRX2*, and *NOL4* were differentially overexpressed in pancreatic origin vs small bowel (Benjamini Hochberg (BH)-corrected $p<0.01$), while *CGA*, *TBC1D30*, and *DTNA* were significantly underexpressed (BH $p<0.01$). *ITGB4* and *CTNNB1* were differentially overexpressed in colon vs other primaries (BH $p<0.05$). Pathway analysis using the “cancer hallmarks”, “gene ontology”, and “KEGG pathway” gene sets in MSigDB, demonstrated that short survival (<2 years) in stage IV NET was associated with marked activation in MYC, oxidative phosphorylation, and ribosome/ribonucleoprotein complex formation pathways and deactivation in G-protein coupled and neuroactive ligand receptor signaling pathways (BH $p<0.00001$). In NETs with ki67>20%, cell cycle mediators (E2F, G2M checkpoint, and MYC), oxidative phosphorylation, and glycolysis pathways were activated, while inflammatory pathways (TNF-alpha, IFN-gamma, and JAK-STAT signaling) were deactivated (BH $p<0.00001$).

In NECs, short survival was associated with marked activation of cell cycle mediators, oxidative phosphorylation, MTOR signaling, and DNA repair pathways, and deactivation of epithelial to mesenchymal transition (EMT), inflammatory (TNF-alpha and IFN-gamma), cell adhesion, and cytokine interaction pathways (BH $p<0.00001$).

CONCLUSIONS

Our analysis revealed differential expression of potentially targetable genes in NECs and NETs. Dysregulation of EMT, TNF α signaling, interferon, and E2F pathways in specific subsets of neuroendocrine malignancies could be used for future precision therapy development.

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