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Tumor-Intrinsic Adaptations to Liver Microenvironment Drive Metastasis in Pancreatic and Small Intestinal Neuroendocrine Tumors

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BACKGROUND

Liver metastasis significantly impacts survival in gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including pancreatic (PNETs) and small intestinal neuroendocrine tumors (siNETs). This study aims to uncover molecular mechanisms driving liver metastasis in these tumors.

METHODS

RNA-seq data from primary and liver metastasis patient samples of PNETs and siNETs were analyzed using publicly available datasets. Differential gene expression (DEG) analysis identified genes with significant expression changes in metastases. Pathway enrichment using hallmark gene sets and MSigDB uncovered key pathways and cell-type-specific processes associated with metastasis. To validate that the observed molecular signatures were tumor-derived, rather than artifacts of contamination by non-tumor liver cells, we applied the ESTIMATE algorithm to assess stromal and immune cell content, confirming tumor purity. Logistic regression-based machine learning models prioritized DEGs with high predictive accuracy (AUC values).

RESULTS

DEG analysis of 83 primary PNETs and 30 liver metastases and 44 primary siNETs and 37 metastases revealed distinct tumor-derived signatures in liver metastases, highlighting upregulation of liver metabolic and inflammatory pathways and downregulation of pancreas- and intestine-specific functions, indicating a phenotypic shift enabling tumor survival in the liver microenvironment. Hallmark pathway enrichment and MSigDB analyses reinforced these findings, emphasizing liver-specific metabolic adaptations. Further, ESTIMATE analysis confirmed high tumor purity in metastatic samples. Logistic regression identified several DEGs with strong discriminatory power (AUC > 0.85) between primary and metastatic tumors. Among these DEGs, two genes, ORM1 (PNET: log2FC = 9.48, AUC = 0.91; siNET: log2FC = 10.38, AUC = 0.95) and CYP2E1 (PNET: log2FC = 8.94, AUC = 0.89; siNET: log2FC = 7.52, AUC = 0.94), were significantly upregulated in both tumor types, suggesting potential roles as biomarkers and therapeutic targets. Ongoing experiments include overexpression and stable knockdown of top DEGs in patient-matched primary tumor- and liver metastasis-derived PNET cell lines, respectively, followed by motility and invasion assays to evaluate their impact on key signaling pathways. Further confirmation and validation of differential expression findings will be performed on in-house constructed tissue microarrays (TMAs) using matched GEP-NET primary and metastatic tumors from our surgical patients.

CONCLUSIONS

This study reveals that liver metastases in GEP-NETs are driven by tumor-intrinsic molecular adaptations, including a shift toward normal liver functions. These findings highlight tumor-specific mechanisms in metastasis and identify key biomarkers with diagnostic and therapeutic potential. This work provides a foundation for precision oncology strategies targeting metastatic GEP-NETs.

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