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Spatial Transcriptomics Reveals Local Subtype-Specific Identity and Signaling within Multifocal Small Intestinal Neuroendocrine Tumors

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BACKGROUND

Small intestinal neuroendocrine tumors (SI-NETs) frequently present as multifocal lesions, but the spatial and molecular mechanisms underlying their development and heterogeneity remain unclear. This study aimed to characterize the phenotypic subtypes of tumor cells across anatomical sites in multifocal SI-NETs and identify local microenvironmental factors influencing tumor development.

METHODS

Spatial transcriptomics was performed on 72 tissue microarray cores derived from four patients with multifocal SI-NETs, that included tumoral and non-tumoral tissues from various anatomical layers of the small intestine and regional metastatic sites. Unsupervised clustering, over-representation analysis (ORA), and ligand-receptor (L-R) pair analysis were used to define tumor subtypes and associated signaling networks. External datasets (GSE98894 and GTEx) were used for validation. Protein expression of selected genes was evaluated by immunohistochemistry.

RESULTS

Unsupervised clustering revealed four major tumor subtypes: mucosal, mesenteric, lymphatic, and deep, based on anatomical location and transcriptomic profiles. Each subtype exhibited distinct gene expression patterns and L-R interactions. The mesenteric and lymphatic subtypes exhibited distinct L-R pairs, such as *NRG1 - ERBB3 (HER3)* and *CXCL12 - CXCR4*, respectively. *5HT - HTR1D* was found in all subtypes except mucosal. Across the four subtypes, *SST - SSTR1/2, PTN - NCL, MDK - NC*L and *GJD2 - GJD2* were consistently detected, suggesting fundamental roles in SI-NET biology.

CONCLUSIONS

While further validation is needed, our findings indicate that multifocal SI-NETs consist of spatially distinct tumor subtypes affected by local cellular interactions, providing insight into SI-NET intra-tumoral heterogeneity, possible microenvironmental-triggered tumorigenesis, and potential subtype-targeted therapeutic strategies.

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