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Gene Expression Changes in Small Bowel Neuroendocrine Tumors Associated with Progression to Metastases

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BACKGROUND: Small bowel neuroendocrine tumors (SBNETs) frequently present with metastases, yet little is known about the molecular basis of this progression. Recognition of important genes could help prognostication or lead to discovery of new targets for therapy. This study sought to identify genes serially differentially expressed between normal small bowel (Nl), primary SBNETs (pSBT) and liver metastases (lMets) to identify expression profiles associated with development of metastases.

METHODS: RNA was isolated from matched Nl tissue, pSBTs and lMets from 12 patients and analyzed with whole transcriptome gene expression microarrays and RNAseq. Changes in gene expression between pSBTs and Nls, lMets and Nls, as well as lMets and were calculated. Common genes that were serially differentially expressed (increasing or decreasing 2-fold from Nl->pSBTs->lMets) were identified, and 10 were validated using qPCR in an additional 40 SBNET patients.

RESULTS: A total of 40 genes (9 upregulated and 31 downregulated) were identified as having 2-fold serial differential expression from Nl through pSBTs to lMets, with 5 upregulated and 5 downregulated selected for validation. Serial differential expression was confirmed by qPCR in 7 of 10 genes, with increasing expression in 2 (ERRFI1, SERPINA10) and decreasing in 5 (DMD, MUC3A, PMP22, SLIT2, TGFBR2). Six genes are involved in neural pathways (growth, synapses,

axonal guidance), 2 in the epidermal growth factor receptor (EGFR), 2 in the AKT, and 1 in the TGF-beta pathway. SYT13 was highly expressed in pSBTs and lMets, with levels 10x higher than those documented for any other tissue in the body.

Conclusion: Recognition of serially increased and decreased gene expression from normal tissues through primary tumors to metastases lends insight into the biology of SBNET progression. Identification of genes involved in this process highlights specific pathways, such as the EGFR and AKT pathways, which can be selectively targeted by new or existing therapeutic agents.