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Differential Protein Expression in Small Intestinal Carcinoids and Liver Metastases

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Background: Small intestinal carcinoids (SICs) are being increasingly detected, yet often late in their clinical course and with metastatic disease. Little is known about the molecular pathways important in the development of metastasis. We have recently developed a Protein Pathway Array to screen for changes in protein and phosphoprotein expression in tissues. The objective of our study was to identify key pathways important in the mechanism of SIC metastasis development.

Methods: From 5 patients undergoing surgical resection for metastatic SIC, tissue was harvested from the primary tumor and adjacent normal small intestine, and from liver metastases and adjacent normal liver from the same patient. Extracted proteins were separated by SDS gel, and Western blots were performed with 136 antibodies. Band densities were determined using BioRad Image system. Significant Analysis of Microarray (SAM) (http://www-stat.stanford.edu/~tibs/SAM/) was used to select the proteins differentially expressed between different groups. Unsupervised hierarchical clustering analysis was performed using BRB Array Tools software v.3.3.0 (htt://linus.nci.nih.gov/BRB-ArrayTools.html).

Results: Of the 136 proteins analyzed, 52 proteins were expressed in these samples. 9 proteins were up-regulated in primary SICs compared with matched normal small bowel mucosa. Cyclin E was down-regulated in primary SIC tissue compared to normal small bowel mucosa. Compared to normal liver tissue, SIC liver metastases demonstrated up-regulation of P-ERK and p27 but down-regulation of CDK2 and CDC25B. When comparing primary

SIC with their paired liver metastases, cyclin E demonstrated a significant up-regulation in the liver metastasis.

Conclusion: Few studies have compared gene or protein expression in primary and metastatic SIC tumors resected simultaneously. Our findings using Protein Pathway Array reveal changes in a limited number of proteins, suggesting that these may be targets for therapy. Future studies are needed to validate these findings.