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Activation of EGFR and c-Met Signaling Pathways in Well-Differentiated Neuroendocrine Tumors of the Small Intestine

E. Liu[1]; K. Mikhitarian[1]; F. Revetta[1]; C. Shi[1]

[1]Vanderbilt University Medical Center, Nashville, TN

Background: Well-differentiated neuroendocrine tumors of the small intestine (SI-NETs) are the second most common malignancy of the gastrointestinal tract only after colorectal carcinoma. Little is known about molecular mechanisms underlying the tumor growth. The purpose of this study is to explore the role of EGFR and c-Met signaling pathways in the pathogenesis of SI-NETs.

Methods: A tissue microarray of primary and metastatic SI-NETs was evaluated by immunohistochemistry for expression of amphiregulin, Her2/neu, EGFR, phosphorylated –EGFR (p-EGFR), c-Met and phosphorylated c-Met (p-c-Met). The microarray contains 9 cases with primary SI-NET and liver metastasis, 20 with primary tumor only, and 6 with liver metastasis only. Activation of EGFR and c-Met was compared between the primary tumors and liver metastases. The correlation of the activation of these two signaling pathways and liver metastatic status was also assessed. Fisher's exact test was used to calculate p values.

Results: Amphiregulin was diffusely expressed in all primary and metastatic SI-NETs. EGFR expression was not detected in any of the tumors. Weak membranous Her2/neu labeling was observed in 18 of 35 (51%) cases. Eleven of 35 (31%) cases were labeled with p-EGFR (activated EGFR). Cytoplasmic and membranous labeling of c-Met was found in almost all cases. However, activation of c-Met (p-c-Met) was only present in 13 of 35 (37%) cases. The activation of c-Met and EGFR was not associated with increased or decreased liver metastasis ($p > 0.05$). In addition, there was no significant difference in p-EGFR and p-c-Met labeling between the primary SI-NETs and liver metastases (see table 1, $p > 0.05$), indicating that the activation of EGFR and c-Met may not play a key role in the different growth pattern of metastatic SI-NETs in the liver.

	Amphiregulin	Her2/neu	pEGFR	c-MET	p-c-Met
Primary NET	28/28 (100%)	13/27 (48%)	8/30 (27%)	30/30 (100%)	9/26 (35%)
Liver Metastasis	15/15 (100%)	7/14 (50%)	3/15 (20%)	14/15 (93%)	4/13 (31%)

Conclusions: Activation of EGFR and c-Met signaling pathways may be involved in tumorigenesis of SI-NETs. However, activation of EGFR and c-Met signaling pathways does not appear to account for the extensive growth pattern of liver metastases from these tumors.