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Expression of Serotonin, FGF2, β-Catenin, E-Cadherin and Cadherin 17 in Primary and Metastatic Well-Differentiated Neuroendocrine Tumors of the Small Intestine

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Background: While most primary well-differentiated neuroendocrine tumors of the small intestine (SI-NETs) remain small and asymptomatic, they can spread to regional lymph nodes and to the liver where they can grow extensively, causing small bowel obstruction and liver failure. Mechanisms underlying the different local behavior of the primary and metastatic tumors have not been elucidated. In this study, we investigate the expression of serotonin, FGF2, β-catenin, E-cadherin and cadherin 17 in primary and metastatic SI-NETs.

Methods: A tissue microarray of primary SI-NETs (n=28) and lymph node metastases (LN-mets, n=24) was assessed by immunohistochemistry for expression of serotonin, FGF2, β-catenin, E-cadherin and cadherin 17. The expression of these molecules was compared between the primary tumors and their corresponding LN-mets. The relationship between their expression in the primary tumors and liver metastatic status was also analyzed.

Results: Serotonin was expressed in a majority of primary SI-NETs (Table 1), with most cases showing a decrease in the LN-Met. FGF2 was expressed in 57% of primary tumors, with LN mets from FGF2-positive primaries showing decreased expression. In addition, 8 of 12 (67%) cases of FGF2-negative primary tumors had liver metastases, whereas only 4 of 16 (25%) cases of FGF2-positive primary tumors had liver metastases (p=0.05, Fisher's exact test). All the primary SI-NETs had β-catenin cytoplasmic and nuclear labeling, with most showing decreased β-catenin labeling in the LN-mets compared to their corresponding primary tumors. The expression of E-cadherin was present in almost all primary SI-NETs but was variable in the LN-mets. Cadherin-17 was strongly expressed in all primary and metastatic SI-NETs. There was no association between liver metastatic status and the expression of serotonin, β-catenin, E-cadherin or cadherin 17 in the primary tumors.

	Serotonin	FGF2	β-catenin	E-cadherin
Primary NET	21/27 (78%)	16/28 (57%)	28/28 (100%)	24/25 (96%)
LN met: No change	1/18 (5%)	2/13 (15%)	4/26 (15%)	12/24 (50%)
Increased	5/18 (28%)			5/24 (21%)
Decreased	12/18 (67%)	11/13 (85%)	22/26 (85%)	7/24 (29%)

Conclusion: Loss of FGF2 expression in primary SI-NETs may be associated with an increased risk for liver metastasis. Decreased serotonin, FGF2 and β-catenin expression was observed in the LN-mets in the majority of the SI-NETs. All SI-NETs and their LN-mets expressed cadherin 17, which is also known to mark other GI carcinomas.