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RUNX1T1: A Novel Predictor of Liver Metastasis in Primary Pancreatic Endocrine Neoplasms

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Background: Clinical outcome of patients with well-differentiated pancreatic endocrine tumors (PETs) and carcinomas (PECAs) is often difficult to predict based on conventional pathologic characteristics. We identified a set of candidate progression genes with differential expression in the primary PECAs with liver metastases relative to non-metastatic primary PETs by using gene expression profiling and validated the selected candidates by real-time-PCR. One of the leading progression genes was RUNX1T1. The aim of this analysis was to validate the differential expression of RUNX1T1 at the protein level on independent test sets of PETs and PECAs, and determine if loss of RUNX1T1 expression was predictive of liver metastases in well-differentiated primary PETs.

Methods: We determined immunohistochemical expression of RUNX1T1 protein in archival PECAs with liver metastases (N=13) and non-metastatic PETs (N=24), using a custom tissue microarray. Allred score (0-8) was used as an independent semi-quantitative measure of RUNX1T1 expression by two pathologists.

Results: RUNX1T1 protein was expressed by all 37 primary tumors, however, median RUNX1T1 Allred score was 2 (range 2-7) in metastatic PECAs compared to a median of 6 (range 3-8) in non-metastatic PETs ($p < 0.0001$). Allred scores of ≤4 were observed in 11 of 13 metastatic PECAs, but in only 1 of 24 non-metastatic PETs ($p < 0.0001$). If an Allred score of ≤4 was considered predictive, the sensitivity of this test for predicting hepatic metastases was 85%, with a specificity of 96%. Low RUNX1T1 expression was highly associated with the presence of hepatic metastases ($p < 0.0001$), while conventional histologic criteria (Ki67 proliferation index, mitotic rate, presence of necrosis) were only weakly associated with metastases ($p = 0.08$-0.15).

Conclusions: RUNX1T1 is differentially expressed in metastatic pancreatic endocrine carcinomas relative to non-metastatic pancreatic endocrine tumors and is a promising marker for prediction of liver metastases in well-differentiated, primary pancreatic endocrine neoplasms.