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Profiling immunohistochemical expression of NOTCH1-3, JAGGED1, cMET, and phospho-MAPK in 100 carcinomas of unknown primary.

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Abstract

Cancer of unknown primary (CUP) is a heterogeneous entity, managed on the basis of "one size fits all" therapeutic concepts; insights into the molecular biology of CUP are urgently needed. We retrospectively examined the immunohistochemical (IHC) expression of Notch1, 2, 3, Jagged1, cMET, and pMAPK biomolecules in 100 CUP tumors using tissue microarrays, aiming to study their correlation to clinicopathologic characteristics and prognostic utility for patient outcome. Notch3 and pMAPK were most frequently expressed (97 and 91 %, respectively). A linear correlation of Notch3 and cMET expression was found ($p = 0.001$), while pMAPK emerged as the major adverse prognostic factor (median overall survival OS 9 vs. 17 months, $p = 0.016$), carrying also a significantly positive predictive value ($p = 0.02$). Our study indicated a favorable prognostic impact of cMET expression in CUP, both in univariate (median OS 15 vs. 9 months, $p = 0.05$) and in multivariate analysis (Relative Risk RR for death 0.48, $p = 0.025$). cMET and Notch3 expression were found to be statistically more frequent in squamous carcinomas (positive in 90 % of cases), associated with a unique metastatic IHC pattern (cMET-high in soft tissue/lymph node metastases, $p < 0.001$, Notch3-high in visceral, peritoneal/pleural and soft tissue/lymph node metastases, $p < 0.001$). Our study points to the MAPK and cMET axes as crucial in defining cancer progression and outcome in CUP patients and, if validated, could justify attempts at their therapeutic modulation.