Ruprecht-Karls-Universität Heidelberg
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Dissertations-Kurzfassung

IGF-1R and TYRO3 as potential biomarkers for response prediction in malignant thymomas and thymic carcinomas treated with sunitinib

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Metastatic and recurrent malignant thymomas (TH) and thymic carcinomas (TC) are generally refractory to current empiric radiochemotherapies, thus warranting the search for novel second-line therapeutic strategies. The multi-target tyrosine kinase inhibitor sunitinib has been shown to induce partial remissions and to prolong overall survival of patients with aggressive TH and TC. However, although sunitinib has been proposed as an alternative treatment option in refractory disease, treatment response is only partial, and not all patients benefit equally. For a more accurate response prediction, new biomarkers are needed.

In this study, we used phospho receptor tyrosine kinase (RTK) and MAPK arrays as well as a multiplex tyrosine phosphorylation assay containing 144 kinase substrates to characterize malignant TH and TC and to generate a sunitinib response index (SRI) using sunitinib resistance-induced cell lines. The RTK and MAPK arrays stratified the patients into two main dominant phosphor patterns: Pattern 1 was characterized by a strong activation of EGFR while pattern 2 was typified by a strong activation of TYRO3/Dtk. This activation of TYRO3/Dtk correlated with recurrence and metastatic spread of malignant TH. p38δ and RSK1 were cluster-specifically activated in the MAPKs but showed no specific disease correlation. The SRI was functionally validated in several cell lines, and the application of the SRI to native malignant TH and TC samples identified a potentially sunitinib-responsive and a potentially sunitinib-resistant group. Among the predicted upstream kinases, TYRO3/Dtk belonged to the top candidates responsible for sunitinib response. TYRO3/Dtk and the highly activated IGF-1R in responsive patients were also functionally validated. Specific siRNA knockdowns in sunitinib-resistant cell lines and overexpression confirmed the functional relevance of TYRO3/Dtk and IGF-1R for sunitinib resistance.

We present the SRI as a new approach to the resistance prediction of sunitinib in malignant TH and TC and propose that the activity level of TYRO3/Dtk and IGF-1R could serve as markers to aid in treatment decisions. The results of this in vitro investigation need validation of the SRI in prospective clinical trials.