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Validation of a fresh-frozen tissue based prognostic gene signature in formalin-fixed, paraffin-embedded melanomas

G. Brunner[1], A. Heinecke[4], L. Suter[1], C. Berking[5], H.-J. Schulze[2] and J. Atzpodien[3]
[1]Cancer Research
[2]Dermatology
[3]Medical Oncology, Skin Cancer Center Hornheide–Münster
[4]Dept. of Medical Informatics and Bioinformatics, Westfälische Wilhelms University of Münster
[5]Dept. of Dermatology and Allergology, Ludwig Maximilians University of Munich, Germany

Histopathological staging of melanoma is limited in predicting outcome, and complementary molecular markers are not available for routine prognostic assessment. We have recently identified and validated a prognostic nine-gene signature expressed in fresh-frozen primary cutaneous melanomas (training cohort: n=91; validation cohort: n=44). A signature-based risk score predicts patient overall survival independently of AJCC staging (multivariate regression analysis: p=0.0004; hazard ratio: 3.8). The purpose of the present study was to establish signature expression analysis in formalin-fixed, paraffin-embedded (FFPE) melanomas to validate prognostic significance of the signature-based risk score.From FFPE melanomas matching the training and validation cohorts of the above study (n=125), RNA was prepared and transcribed into cDNA. Following cDNA pre-amplification, expression of the 9 signature genes, 2 additional candidate genes, and 3 housekeeping genes was quantified by real-time PCR. Correlation of gene expression with overall survival was evaluated using cox regression analysis. Expression of a signature of 8 out of 11 genes was significantly associated with overall survival in univariate cox regression analysis. A signature based risk-score predicted overall survival independently of AJCC staging (multivariate analysis: p=0.007, hazard ratio 3.0). Thus, the fresh-frozen tissue based prognostic gene signature was successfully validated in FFPE melanomas.We have established a quantitative, robust prognostic score, based on FFPE melanomas, that is complementary to AJCC in predicting outcome. This greatly increases clinical applicability and allows retrospective prognostic assessment of melanomas. The score identifies patients at low risk, not identified by AJCC staging, and defines high-risk patients in need of adjuvant therapy.

Biography

G. Brunner has completed his Ph.D. in Germany and postdoctoral studies at the German Cancer Research Center in Heidelberg. He spent more than 8 years abroad, as Research Assistant Professor at NYU and lecturer at Manchester University in the UK. He is the Head of Research at the Skin Cancer Center Hornheide-Münster in Germany. He has published more than 50 papers in reputed journals and is inventor on 3 international patents.

georg.brunner@fachklinik-hornheide.de

In silico designing of dual TxS inhibition and TPR antagonism

Abhay Krishna and Arpita Yadav
CSJM University, India

Thromboxane A2 (TxA2) is one of the key signalling molecules involved in inflammation, platelet aggregation and other important physiological regulations. Inhibition of TxA2 synthesis can therefore be utilized for designing anti-inflammatory drugs and drugs for venous thromboembolism. Thromboxane receptor (TPR) antagonists and thromboxane A synthase (TxS) inhibitors have not been clinically successful so far. The acceptance of a variety of substrates by TPR adds to the problems apart from pharmacokinetic issues. TxS inhibition can lead to a build up of PGI_2 that can activate TPR as well. Utilizing synergistic effect of TxS inhibition and TPR antagonism is therefore a better option. This study utilizes molecular modeling and docking to explain drug-receptor interactions at thromboxane synthase active site and also interactions of antagonists with TPR binding site. Role of heme in TxS inhibitor is also highlighted. An attempt has been made at utilizing natural lead compound bromelaine for designing dual inhibitor of TxAS and TPR to benefit from their synergistic actions.

abhaykrishna51@gmail.com, arpitayadav@yahoo.co.in

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