Carola Henrike Schrader

Dr. med. dent

**Expression and Function of Kallikrein 6 in the Pathogenesis of Head and Neck Squamous Cell Carcinoma**

Fach/Einrichtung: Hals-Nasen-Ohrenheilkunde

Doktorvater: PD Dr. Jochen Heß

Aberrant expression of Kallikrein-related peptidase 6 (KLK6) is a common feature in many human cancers. Nevertheless, in head and neck squamous cell carcinoma (HNSCC) KLK6 expression and its molecular function have not been investigated so far. Tissue microarrays with tumour specimens of primary HNSCC were investigated by immunohistochemical staining, and the correlation between KLK6 protein levels and survival was assessed by Kaplan-Meier and multivariate Cox proportional hazard model analysis. High KLK6 protein expression in a laryngeal squamous cell carcinoma (LSCC) patient cohort (n=47) was significantly correlated with improved overall (p-value 0.013) and progression-free survival (p-value 0.012). Similar results were obtained for a combined cohort of LSCC and oropharyngeal SCC (OPSCC) (n=162) with increased overall survival (p-value <0.0005) and progression-free survival (p-value 0.001) for HNSCC patients with high KLK6 expression. Furthermore, patient's clinical pathological data was analysed for correlations to KLK6 expression. Multivariate Cox proportional hazard model analysis verified that KLK6 serves as an independent risk factor for a favourable clinical outcome in both cohorts. To unravel the role of KLK6 in the pathogenesis of HNSCC, cell culture experiments were conducted using HNSCC cell lines. KLK6 expression was detected in the HNSCC cell lines FaDu, Cal27 and SCC25, but not in HeLa cervix carcinoma cells. As a loss-of-function approach, FaDu clones with stable silencing of KLK6 expression were generated by shRNA technology, and revealed accelerated cell cycle progression as well as increased cell mobility. Moreover, FaDu clones with silenced KLK6 expression displayed molecular features resembling epithelial-to-mesenchymal transition (EMT) and exhibited higher resistance against irradiation. As proof of principle, already existing HeLa cell clones with ectopic KLK6 expression were analysed to confirm the mode of action of KLK6 expression on tumour cells.

Numerous studies evaluated KLK6 as a promising biomarker for early diagnosis or unfavourable prognosis. The present study demonstrates for the first time that low KLK6 expression serves as an unfavourable risk factor for progression-free and overall survival of HNSCC patients, suggesting a context-dependent role of KLK6 in different human tumour entities. In summary, detection of low KLK6 expression in primary tumours represents a promising new tool to stratify HNSCC patients with a high risk for treatment failure, who might benefit from restoration of KLK6 expression.