Frederik Otto Werner Bartels
Dr. med.

Functional Characterization of the Lysosomal Protein Transmembrane 5 as a Potential Tumor Suppressor Gene in Glioblastoma

Einrichtung: DKFZ (Deutsches Krebsforschungszentrum)
Doktorvater: Prof. Dr. med. Wolfgang Wick

Glioblastoma is associated with a poor prognosis due to its malignant biological features including a high invasive and migratory potential. A whole-genome *in vivo* screen using a RNA interference (RNAi) library was performed in order to detect potential genes regulating glioblastoma cell invasion. One of the candidate genes identified was the Lysosomal Protein Transmembrane 5 (LAPTM5). The aim of this study was to further characterize the role of LAPTM5 in glioblastoma biology on a functional and molecular level.

A knockdown model of LAPTM5 in the U87MG cell line showed that LAPTM5 inhibits glioblastoma invasiveness and clonogenicity *in vitro*, as well as tumor growth *in vivo*. Furthermore, *in vitro* and *in vivo* experiments revealed that LAPTM5 sensitizes glioblastoma cells to temozolomide, the standard chemotherapy used in the treatment of glioblastoma patients. Microarray analysis identified the NF-kB signaling pathway to be inhibited by LAPTM5 in glioblastoma, which was subsequently confirmed by functional experiments. The effects of LAPTM5 on glioblastoma cell invasion were mediated by the NF-kB signaling pathways as well as by a target of the MMP-inhibitor batimastat (BB94).
LAPTM5 expression in glioblastoma was found to be silenced by methylation both *in vitro* and in human glioblastoma samples. Moreover, low LAPTM5 expression in human glioblastoma samples was associated with reduced patient survival.

Together, these findings suggest that LAPTM5 is a potential tumor suppressor gene in glioblastoma acting via inhibition of the NF-kB signaling pathway. This implicates that LAPTM5 activation might be a promising new target in glioblastoma therapy reducing tumor cell invasion and tumor growth as well as sensitizing glioblastoma cells to temozolomide chemotherapy. Further studies on the role of LAPTM5 as a potential tumor suppressor gene are warranted.