Bildgebend-gesteuerte Gentherapie maligner Gliome

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Malignant gliomas are the most common intracranial neoplasms that occur with an incidence of ~6 per 100,000 per year. Glioblastoma multiforme – as the most malignant grade of glioma – accounts for about 50% of gliomas and is associated with a dismal prognosis and poor quality of life. Despite vast efforts, development of novel therapeutic approaches has been disappointing in past years. In gene-directed enzyme prodrug therapy, or “suicide gene therapy”, tumor cells are transduced with a gene coding for a certain enzyme that metabolizes a non-toxic prodrug, given systemically to the patient, to a toxic drug that then selectively destroys the transduced tumor cells and some surrounding tissue through bystander effects. This dissertation summarizes our advancements in suicide gene therapy in the early years of the 21st century. Under the hypothesis that tumor cells derived from brain tumors of individual patients could be transduced with our specific Herpes simplex virus 1 amplicon vector, we first performed a cell culture study on the biopsy material from 42 brain tumor patients, showing that transduction efficiency of more malignant tumor types was significantly lower (11.2 %) than that of the lower-grade tumors (26.7 %, $p < 0.05$). We next aimed to visualize both transgene expression as well as therapeutic efficacy in vivo in order to establish a therapeutic approach that could be translated into the clinic. Using Positron Emission Tomography (PET), we confirmed transgene expression – as assessed by 9-(4-[18F]fluoro-3-hydroxymethylbutyl)-guanine ([18F]FHBG)-PET – to correlate the induced therapeutic effects – as assessed by 3’-deoxy-3’-[18F]fluorothymidine ([18F]FLT)-PET ($R = 0.73$, $p < 0.01$). In a third study, we additionally demonstrated that the level of vector-mediated gene expression exactly correlated to the induced therapeutic effects ($R = 0.72$, $p < 0.01$). Since literature suggests that malignant gliomas derive from undifferentiated stem cells residing in the adult mammalian brain, but those endogenous neural stem cells (NSC) constitute a key effector population in the field of regenerative medicine, we next aimed to mobilize the endogenous NSC niche without causing glioma. The fourth publication of this dissertation firstly describes a non-canonical Notch signaling pathway that specifically mobilizes NSC in vitro and in vivo without inducing cancer. The novel therapeutic approaches summarized in this dissertation have since been further advanced towards clinical studies, demonstrating their high relevance in neurooncology.