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Meeting Abstract

Target-specific glioma therapy in an immunocompetent mouse model

Targetspezifische Gliomtherapie in einem immunkompetenten Mausmodell

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Text

Objective: Establishment of an immunocompetent mouse model representing the typical progressive stages observed in malignant human gliomas for the *in vivo* evaluation of novel target-specific regimens.

Methods: Isolated clones from tumours that arose spontaneously in GFAP-v-*src* transgenic mice were used to develop a transplantable brain tumour model

in syngeneic B6C3F1 mice. STAT3 protein was knocked down by infection of tumour cells with replication-defective lentivirus encoding STAT3-siRNA. Apoptosis is designed to be induced by soluble recombinant TRAIL + chemical Bcl-2/Bcl-xL inhibitors.

Results: Striatal implantation of 10^5 mouse tumour cells resulted in the robust development of microscopically (2 – 3 mm) infiltrating malignant gliomas. Immunohistochemically, the gliomas displayed the astroglial marker GFAP and the oncogenic form of STAT3 (Tyr-705-phosphorylated) which is found in many malignancies including gliomas. Phosphorylated STAT3 was particularly prominent in the nucleus but was also found at the plasma membrane of peripherally infiltrating glioma cells. To evaluate the role of STAT3 in tumour progression, we stably expressed siRNA against STAT3 in several murine glioma cell lines. The effect of STAT3 depletion on proliferation, invasion and survival will be first assessed *in vitro* and subsequently after transplantation *in vivo*. Upstream and downstream components of the STAT3 signalling pathway as well as possible non-specific side effects of STAT3-siRNA expression after lentiviral infection will be examined, too.

Conclusions: Its high rate of engraftment, its similarity to the malignant glioma of origin, and its rapid locally invasive growth

should make this murine model useful in testing novel therapies for malignant gliomas.