YB-1 dependent virotherapy in combination with temozolomide as a multimodal therapy approach to eradicate malignant glioma.

Abstract:
The human Y-box binding protein 1 (YB-1) is known to be a promising target for cancer therapy. We have demonstrated that YB-1 plays an important role in the adenoviral life cycle by regulating the adenoviral E2-gene expression. Thus, we studied the oncolytic effect of the recombinant adenovirus Ad-Delo3-RGD, in which the transactivation domain CR3 of the E1A protein is ablated to enable viral replication only in YB-1 positive cancer cells. In vitro Southern Blot analysis and cytopathic effect assays demonstrate high anti-glioma potency, which was significantly increased in combination with temozolomide (TMZ), daunorubicin and cisplatin. Since vascular endothelial growth factor (VEGF) is thought to promote the hypervascular phenotype of primary, malignant brain tumors, we also tested Ad-Delo3-RGD in regard to the inhibition of VEGF expression. Indeed, we found that Ad-Delo3-RGD induced VEGF down regulation, which was even amplified under hypoxic conditions. Tumor-bearing nude mice treated with the YB-1 dependent oncolytic adenovirus showed significantly smaller tumors than untreated controls. Furthermore, combination therapy with TMZ led to a regression in all treated animals with complete tumor regression in 33 % of analyzed mice, which was verified by bioluminencescence imaging and
histological studies. In addition, histopathological evaluation revealed enhanced apoptosis and a
reduction in tumor vessel formation, indicating that Ad-Delo3-RGD has an anti-angiogenic effect in
addition to its oncolytic capacity in vivo. Hence, our results demonstrate that the combination therapy
of YB-1 dependent virotherapy and TMZ is effective in a xenograft glioma mouse model and might be
useful in a YB-1 based clinical setting.