Dokumenttyp: journal article

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Abstract: We investigated the novel recombinant oncolytic adenovirus Ad-delo-sr39TK-RGD, armed with a mutant herpes simplex virus type 1 thymidine kinase (HSV1-sr39TK) as a suicide gene, and explored its antitumor efficacy in combination with HSV1-sr39TK/ganciclovir (GCV) gene therapy and temozolomide (TMZ). Ad-delo-sr39TK-RGD is an E1-mutated conditionally replicating adenovirus dependent on the human Y-box binding protein 1 (YB-1). Thus, we utilized the YB-1 dependency of the vector to target human glioma cells in vitro, using two-dimensional cell culture and three-dimensional multicellular spheroids, and demonstrated the strong replication competence and oncolytic potential of the virus. The cytotoxicity mediated by HSV1-sr39TK and its prodrug GCV enhanced the oncolytic effect even at 95% after adding GCV 0-1 days following infection. An increased bystander effect of viral replication and GCV in co-cultured infected and uninfected cells was observed. Co-administrating Ad-delo-sr39TK-RGD with TMZ and GCV, spheroid growth was reduced drastically. Gamma counting of infected spheroids demonstrated successful accumulation of the radiotracer (18)F-labeled 9-[4-fluoro-3-(hydroxymethyl)butyl]guanine mediated by HSV1-sr39TK. Hence, our results show that the combination of YB-1-dependent virotherapy with
suicide genes and TMZ effectively induces glioma cell killing and may allow for in vivo non-invasive imaging within a limited time frame.