A Novel Attenuated Replication-Competent Adenovirus for Melanoma Therapy

Summary / Zusammenfassung
To generate a replication-competent adenovirus (Ad) with specificity for melanoma, we constructed a tissue specific promoter restricting E1A expression to such target cells. The combination of four copies of a mouse tyrosinase enhancer element (TE) fused to the human tyrosinase promoter (TP) yielded up to 2000-fold higher luciferase reporter activity in tyrosinase-expressing melanoma cells than in non-melanoma cells. Insertion of the TETP construct into an E3-deleted Ad upstream of E1A yielded preferential, though not exclusive E1A expression in melanoma cells, possibly due to remaining Ad control sequences. In a novel approach, the specificity of E1A expression was considerably enhanced by specifically deleting the intertwined endogenous Ad enhancer/promoter (EP) sequences upstream of E1A, while leaving the DNA packaging signals intact. This virus (Ad*EP-TETP) replicated at efficiencies comparable to wild-type (wt) Ad5 in tyrosinase-positive melanoma cells, such as SK-Mel23 but more than 50-fold less in non-melanoma tumor cells and primary human cells. Injection of Ad*EP-TETP into xenotransplanted melanomas but not HeLa-derived tumors led to long-lasting tumor regression in nude mice. Our results emphasize that the replication of Ad vectors can be tailored at the promoter level to boost the selective oncolytic viral activity, a key feature for a safe and effective cancer therapy.

Publications / Publikationen
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