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TITLE & ABSTRACT:

Adenoviral gene therapy for ovarian cancer

Conditionally replicating adenoviruses (CRAds) represent a novel approach for treating cancer. However, their oncolytic potency is determined by their capability of infecting target cells. As most Ad vectors and CRAds are based on serotype 5 (Ad5), which binds to the coxsackie-adenovirus receptor (CAR), lack of CAR could make target tissues refractory. Indeed, recent data suggest that CAR expression in tumors is highly variable. Therefore, methods to circumvent CAR-deficiency have been evaluated. In our studies, we explored substituting the receptor binding fiber knob domain of Ad5 vector with the serotype 3 knob. This resulted in CAR-independent infection, as Ad3 has a distinct, but unidentified receptor. Importantly, this serotype chimerism was a useful means of enhancing infectivity. Further, the murine liver toxicity, blood clearance and biodistribution profiles were comparable to Ad5. Therefore, we created an Ad3 receptor retargeted CRAd, Ad5/3-D24. This oncolytic virus has a 24-bp deletion in the E1A, which restricts the replication in cancer cells inactive in the Rb pathway. We compared Ad5/3-D24 to the non-fiber modified isogenic control virus and showed faster replication of Ad5/3-D24 and subsequent oncolysis of ovarian cancer lines. Replication was also analyzed with quantitative PCR on patient samples. Moreover, in an orthotopic model, dramatically enhanced survival was noted with Ad5/3-D24. Using in vivo bioluminescence imaging, we were able to detect the intraperitoneal ovarian cancer cell killing by the virus. Another possible approach for analyzing efficacy in vivo could be a CRAd expressing an inert soluble marker peptide, which can be measured from serum. Consequently, we constructed Ad5/3-D24-hCEA, which features a secreted marker protein, soluble human carcinoembryonic antigen (hCEA). We found that virus replication closely correlated with hCEA secretion. Further, antitumor efficacy and persistence of the virus could be deduced from plasma hCEA levels. Finally, using in vivo bioluminescence imaging, we were able to detect effective tumor cell killing by the virus, which led to enhanced therapeutic efficacy and increased survival of mice with disseminated ovarian cancer.

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