Therapeutic Effects of RGD-Fiber Modified E1A, E1B Double-Restricted Oncolytic Adenovirus for CAR-Deficient Bladder Cancer

Introduction and Objectives: We have previously demonstrated that an E1A, E1B double-restricted oncolytic adenovirus AxdAdB-3 has a potential antitumor effect on an orthotopic bladder cancer model in severe combined immunodeficiency (SCID) mice. In the present study, we evaluate the therapeutic efficacy of AxdAdB-3 with RGD-fiber modification (AxdAdB3-F/RGD), which enables integrin-dependent infection, for bladder cancer.
Material and Methods: Expressions of adenoviral receptors, coxsackievirus adenovirus receptor (CAR) and integrins ($\alpha_v\beta_3$ and $\alpha_v\beta_5$) were detected in human bladder cancer cell lines YTS-1, T24, 5637 and KK47. Adenovirus-mediated gene transduction into various cell lines was evaluated by AxCAlacZ (LacZ-expression replication-defective adenoviurs) or AxCAZ3-F/RGD (LacZ-expression replication-defective adenovirus with RGD-modified fiber) infection followed by 5-bromo-4-chloro-3-indolyl-beta-galactoside (X-Gal) staining. The cytopathic effects of AxdAdB3-F/RGD were evaluated in several bladder cancer cell lines and in a normal bladder mucosa-derived cell line (HCV29) with AxCAZ3-F/RGD (control) or AxdAdB-3. The efficacy of bladder instillation therapy with AxdAdB3-F/RGD for orthotopic bladder cancer of nude mice was investigated.
Results: The susceptibility of various cell lines to adenovirus was associated with the expression of CAR, whereas all the bladder cancer cell lines tested expressed integrins ($\alpha_v\beta_3$ or $\alpha_v\beta_5$). AxdAdB-3 was more cytopathic in CAR-positive bladder cancer cells than in CAR-negative cells, whereas AxdAdB3-F/RGD caused the potent oncolysis in both CAR-positive and CAR-negative bladder cancer cells. AxdAdB3-F/RGD was not cytotoxic against HCV29. Direct instillation of AxdAdB3-F/RGD into the bladder of the orthotopic model established by CAR-deficient human bladder cancer cells inhibited tumor growth, leading to significantly prolonged survival.
Conclusions: E1A, E1B double-restricted oncolytic adenovirus with RGD-fiber modification enhanced the infectivity and oncolytic effects to CAR-deficient bladder cancer while sparing normal cells, our results demonstrate the therapeutic potential of AxdAdB3-F/RGD for bladder cancer.