TARGETED GENE THERAPY FOR CANCERS BY USING Z33 FIBER MODIFIED ADENOVIRUS VECTOR WITH TUMOR SPECIFIC ANTIBODIES

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Although adenovirus is widely used for cancer gene therapy, conventional adenoviral vectors infect not only cancer cells but also normal cells. Therefore, a new method that allow targeted gene delivery to cancer cells needs to be developed to obtain more efficient anti-tumor effect and safety. We constructed an adenovirus incorporating an IgG Fc binding motif from the Staphylococcus protein A (Z33). This vector with tumor specific antibody enables antibody-dependent selective gene delivery. Cancers of biliary systems are highly malignant diseases with poor prognosis and thus development of new treatments such as gene therapy is necessary. [AIM] We aimed to explore methods of selective gene therapy to biliary cancers using the Z33 fiber modified adenovirus with several tumor specific antibodies (epithelial cell adhesion molecule (EpCAM), epidermal growth factor receptor (EGFR), erbB2). [METHODS] We examined three lines of BC (KMC-1, 1TKB, 2TKB). Two lines (HepG, HuH-7) of hepatocellular carcinoma (HCC), Hela cells, and primary normal hepatocytes were used as controls. Expressions of EpCAM, EGFR, and erbB2 were analyzed by FACS. Expressions of EpCAM, EGFR, and erbB2 were analyzed by FACS. Gene transduction efficiency was examined by a Z33-fiber modified adenovirus expressing LacZ, followed by β-gal assay. Efficacy of this system as a cancer gene therapy was evaluated by whether a Z33-fiber modified adenovirus expressing UPRT (uracil phosphoribosyl transferase), an enzyme which enhances the toxicity of 5-fluorouracil (FU), can alter the sensitivity of cancer cells to 5-FU. Efficacy in vivo was tested in nude mice with subcutaneously xenografts of BC cells. [RESULTS] Both BC lines (1TKB, 2TKB and KMC-1)and HCC lines (HepG2 and HuH-7) demonstrated expressions of EpCAM and EGFR at high levels. When specific antibodies to EpCAM or EGFR were used in combination with Z33-fiber modified adenovirus, improved high efficiencies of gene transduction were achieved, compared with when control antibody was used, in BC cells. ErbB2 was also highly expressed in BC lines (44TKB and KMC-1) and some HCC lines (HepG2 and HuH-7), but the gene transduction did not improve by using specific antibodies to erbB2 in combination with Z33-fiber modified adenovirus. The Z33-fiber modified adenovirus expressing UPRT coupled with anti-EpCAM or anti-EGFR antibodies remarkably enhanced the sensitivity of BC (1TKB and KMC-1) cells, but did not effect the sensitivity of normal hepatocytes, to 5-FU. Finally, the Z33-fiber modified adenovirus expressing UPRT coupled with anti-EpCAM or anti-EGFR antibodies, followed by 5-FU administration, completely inhibited the growth of tumors in nude mice. [CONCLUSIONS] The Z33 fiber modified adenovirus in combination with tumor specific antibodies (anti-EpCAM, anti-EGFR) enables specifically targeted gene therapy to biliary cancers. This approach is not only easy and versatile, but it can also combine gene therapy approaches with a variety of molecular targeted antibody therapies for cancers to obtain potent anti-tumor efficacy.