Adenoviral vector specifically targeted to EphA2 receptor in pancreatic cancer cells

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Pancreatic cancer is a devastating disease with poor prognosis. This warrants the development of novel therapies including gene therapy. However, clinical studies have demonstrated poor efficacy of adenoviral gene therapy because of the absence of adenoviral binding sites on pancreatic cancer cells such as the coxsackie and adenovirus receptor (CAR). Circumventing CAR-mediated entry therefore seems a promising option to improve adenoviral entry into pancreatic cancer cells and to enhance the efficacy of adenoviral vectors.

A research team led by Dr. Piter J Bosma from University of Amsterdam addressed this question. Their study will be published on June 14, 2009 in the World Journal of Gastroenterology.

They present a novel adenoviral vector that binds to the EphA2 receptor (EphA2R). This receptor is highly expressed in several solid tumors including pancreatic cancer. YSA, a small peptide ligand that binds the EphA2R with high affinity, was inserted into the HI loop of the adenovirus serotype 5 fiber knob. To further increase the specificity of this vector, binding sites for native adenoviral receptors, the coxsackie and adenovirus receptor (CAR) and integrin, were ablated from the viral capsid. The ablated retargeted adenoviral vector was produced on 293T cells. Specific targeting of this novel adenoviral vector to pancreatic cancer was investigated on established human pancreatic cancer cell lines. Upon demonstrating specific in vitro targeting, in vivo targeting to subcutaneous growing human pancreatic cancer was tested by intravenous and intraperitoneal administration of the ablated adenoviral

vector.

They found that ablation of native cellular binding sites reduced adenoviral transduction at least 100-fold. Insertion of the YSA peptide in the HI loop restored adenoviral transduction of EphA2R-expressing cells but not of cells lacking this receptor. YSA-mediated transduction was inhibited by addition of synthetic YSA peptide. The transduction specificity of the ablated retargeted vector towards human pancreatic cancer cells was enhanced almost 10-fold in vitro. In a subsequent in vivo study of a nude (nu/nu) mouse model however, no increased adenoviral targeting to subcutaneously growing human pancreas cancer nodules was seen upon injection into the tail vein, nor upon injection into the peritoneum.

Although re-directing of the adenoviral vector has been reported, this is the first paper showing effective uptake of adenoviral vector by the EphA2R that is present on solid tumors.

More information: van Geer MA, Bakker CT, Koizumi N, Mizuguchi H, Wesseling, JG, Oude Elferink RPJ, Bosma PJ. Ephrin A2 receptor targeting does not increase adenoviral pancreatic cancer transduction in vivo. *World J Gastroenterol* 2009; 15(22): 2754-2762 Available, from: URL: www.wjgnet.com/1007-9327/15/2754.asp

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