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Tumor Specific Targeting of Adenoviral Vectors to Cancer

A. Deisseroth, L. Zhang, Y.C. Tang, Y.Z. Liu, J. Maynard, I. Chung, J.H. Won, D.B. Shin, H. Akbulut

Sidney Kimmel Cancer Center, San Diego, CA, USA

Abstract

Adenoviral vectors have been used to deliver therapeutic transcription units to epithelial malignancies for short term modification of these cells for therapy. The adenoviral vector is an attractive choice since it infects most epithelial cells (normal and neoplastic), and expresses its transgenes in cells which are non-dividing as well as dividing. The expression of the therapeutic transgenes in the normal cells can generate toxicity and the expression of the CAR receptor, which is necessary for infection, on the surface of the tumor cells is variable in cancer. In addition, the use of replication incompetent adenoviral vector has the theoretical limitation of incomplete infection of the target tumor cells. In order to create an adenoviral vector which is more selective and more potent, I. Chung in our laboratory truncated the L-plastin promoter and showed that when it is introduced into the adenoviral backbone, that it drives the expression of therapeutic transgenes in a tumor specific manner. X.Y. Peng, L. Zhang, and H. Akbulut then showed that when the L-plastin promoter is placed 5' of the viral replication gene E1A or the chemotherapy sensitization gene, cytosine deaminase (CD) in an adenoviral vector, infected breast or ovarian cancer cells are destroyed, whereas normal breast or ovarian epithelial explant cultures are resistant to the toxic effect of these vectors. L. Zhang and H. Akbulut showed that the L-plastin promoter driving the expression of a bicistronic transcription unit composed of the CD gene linked to the E1A gene was more toxic than adenoviral vectors carrying only a single therapeutic gene under the control of the L-plastin promoter. We are currently studying the effect of adding chemotherapy to the infection of tumor cells with these vectors, and also engineering the fibrillar protein of the vector so as to direct its infection more specifically to the tumor cells.