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Preclinical evaluation of transcriptional targeting strategies for carcinoma of the breast in a tissue slice model system

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Abstract

Introduction In view of the limited success of available treatment modalities for metastatic breast cancer, alternative and complementary strategies need to be developed. Adenoviral vector mediated strategies for breast cancer gene therapy and virotherapy are a promising novel therapeutic platform for the treatment of breast cancer. However, the promiscuous tropism of adenoviruses (Ads) is a major concern. Employing tissue specific promoters (TSPs) to restrict transgene expression or viral replication is an effective way to increase specificity towards tumor tissues and to reduce adverse effects in non-target tissues such as the liver. In this regard, candidate breast cancer TSPs include promoters of the genes for the epithelial glycoprotein 2 (EGP-2), cyclooxygenase-2 (Cox-2), α-chemokine SDF-1 receptor (stromal-cell-derived factor, CXCR4), secretory leukoprotease inhibitor (SLPI) and survivin.

Methods We employed E1-deleted Ads that express the reporter gene luciferase under the control of the promoters of interest. We evaluated this class of vectors in various established breast cancer cell lines, primary breast cancer cells and finally in the most stringent preclinical available substrate system, constituted by precision cut tissue slices of human breast cancer and liver.

Results Overall, the CXCR4 promoter exhibited the highest luciferase activity in breast cancer cell lines, primary breast cancer cells and breast cancer tissue slices. Importantly, the CXCR4 promoter displayed a very low activity in human primary fibroblasts and human liver tissue slices. Interestingly, gene expression profiles correlated with the promoter activities both in breast cancer cell lines and primary breast cancer cells.

Conclusion These data suggest that the CXCR4 promoter has an ideal 'breast cancer-on/liver-off' profile, and could, therefore, be a powerful tool in Ad vector based gene therapy or virotherapy of the carcinoma of the breast.

Introduction

Breast cancer is the most common cancer in the world. It affects 1 in 9 women in the United States where 46,000 women die from breast cancer each year despite early detection methods and advanced conventional treatments [1]. Clearly, novel therapies for breast cancer are required. Gene therapy and virotherapy constitute a novel therapeutic approach for the treatment of advanced, recurrent and metastatic breast cancer. In gene therapy approaches, a therapeutic gene for mutation compensation, immunopotentiation, or

Ad = adenovirus; BSA = bovine serum albumin; CAR Coxsackie-Adenovirus-Receptor; CMV = cytomegalovirus; Cox = cyclooxygenase; CXCR4 = α-chemokine SDF-1 receptor; DAPI = 4',6-diamidino-2-phenylindole dihydrochloride; EGP = epithelial glycoprotein; FCS = fetal calf serum; GAPDH = glyceraldehyde-3-phosphate dehydrogenase; MOI = multiplicity of infection; PBS = phosphate-buffered saline; PCR = polymerase chain reaction; SLPI = secretory leukoprotease inhibitor; TSP = tissue specific promoter; UAB = University of Alabama at Birmingham; UW = University of Wisconsin.