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Enhancement of Anti-tumorigenicity by Cytokine and Costimulus Gene Transfer in Animal Tumor Models

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Treatment of tumor by conventional way (surgery, irradiation, chemotherapy) is limited by lack of specificity and excessive toxicity. One of the advanced tries is gene therapy. Gene therapy is receiving considerable attention as a method of delivering immunosensitizing, chemosensitizing and tumoricidal substance to tumors. In this presentation, I would like to introduce two examples of gene transfer in animal tumor models; one is in the brain tumor formation by IL-2 and the other in the hepatoma by GM-CSF and B7-2.

Interleukin-2 (IL-2) is known to be secreted by T helper cells and to stimulate cytotoxic T cells and natural killer cells, affecting antitumor responses. The antitumor effects of IL-2 were examined in rats implanted with 9L glioma cells. As a delivery vehicle of IL-2, rat brain endothelial cells (RBEZ) were used. RBEZ-IL2 cells were obtained by transfection with pBCMG-hygro-IL2, a BPV expression vector containing murine IL-2 cDNA under the transcription control of a cytomegalovirus promoter. 9L cells were injected stereotactically into left cerebral hemispheres concurrent with either RBEZ-hygro (control) or RBEZ-IL2 cells, and tumor formation was determined. The results establish that genetically modified endothelial cells can be stably engrafted to growing gliomas and effectively deliver antitumor agents.

GM-CSF is the most potent, specific and long-lasting inducer of antitumor immunity. The enhancement of immune function mediated by costimulatory molecules such as B7-1 and B7-2 plays an important role in the induction of T cell-mediated antitumor immunity. We constructed the pLSN vector system to contain neomycin-resistant gene and CMV promoter. The pLSNGM, pLSNB7 and pLSNBG, pLSN vectors each containing hGM-CSF, B7-2, both hGM-CSF and B7-2 cDNA respectively, were constructed. They were transfected into human hepatoma cell line (SK-HEP1), and the expressions were determined in individual transfected cells by ELISA, FACS, and RT-PCR. We selected stable transfected cells expressing high levels of hGM-CSF and costimulatory molecule of B7-2. We observed that pLSNBG transfectant cells displayed more elongated processes and attachable characteristics than control SK-HEP1 cells. To understand the growth characteristics of the transfectants, we measured the cell proliferation. The pLSNGM and pLSNB7 cells were shown to be similar growth pattern, comparing with pLSN cells. However, pLSNBG cells growed much faster than pLSNGM and pLSNB7 cells. Primary cytolytic activity was significantly induced in pLSNBG cells. In vivo experiments, pLSNMG, pLSNB7, and pLSNBG transfectant cells showed much less subcutaneous tumor formation, comparing with control cells. These findings suggested that these strategies may provide a clue to treat tumor.