

2. Non-technical Abstract

Cancer may become the leading cause of death in the US in the next 10-20 years. The incidence of malignant melanoma is rising most rapidly at an annual rate of 4 % than any other types of cancer. Huge progress has been made in recent years in understanding of genetic basis of cancer. However, the treatment of cancer is still basically dependent on the early detection and surgical removal followed with chemotherapy and radiation therapy. This standard therapeutic approach is limited by anatomical location, by toxicity of most of chemotherapeutic agents and radiation, and by the resistance of cancer cells such as malignant melanoma to these agents. Systemic use of recombinant cytokines has been in use to treat cancer patients. But its limitation is severe side effects of many cytokines and the complexity of cytokine network. Lymphokine (IL-2)-activated killer (LAK) cells or tumor-infiltrating lymphocytes (TIL) have been successfully used in clinical trials. Both types of cells need to be activated with IL-2 which has an undesirable side effect (vascular leak syndrome). Cytokine gene therapy avoids the toxicity problems associated with systemic use of recombinant cytokines or IL-2-expanded LAK or TIL cells. Remarkable effectiveness as tumor vaccine shown in our mouse experimental model warrants further studies of GM-CSF-gene therapy, which could become an alternative approach to the treatment of cancer. Many previous studies used irradiated GM-CSF-producing tumor cells as vaccine with the varying degree of the anti-tumor activities. Most of these studies used retroviral vectors to transduce the autologous tumor cells. Our approach to utilize

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replication incompetent recombinant adenoviruses harboring GM-CSF has not been commonly used in preclinical as well as clinical studies. Adenoviral vector offers definitive advantages over retroviral vector, because of higher degree of expression of desired gene by transduced cells and avoidance of gene inactivation due to positional or methylation effect, which sometimes occurs with retroviral delivery of genes. The disadvantage of adenoviral vector is that GM-CSF cDNA does not integrate into host DNA and is therefore expressed only transiently. The proposed study will be extremely important to analyze the adaptability of the adenovirus-based tumor cell vaccine and to form the basis for future clinical trials.