学 位 論 文 の 要 旨

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主論文の題名

Systemic CD8+ T Cell-mediated Tumoricidal Effects by Intratumoral Treatment of Oncolytic Herpes Simplex Virus with the Agonistic Monoclonal Antibody for Murine Glucocorticoid-induced Tumor Necrosis Factor Receptor

主論文の要旨

Oncolytic virotherapy combined with immunomodulators is a novel noninvasive strategy for cancer treatment. In this study, we examined the tumoricidal effects of oncolytic HF10, a naturally occurring mutant of herpes simplex virus type-1, combined with an agonistic DTA-1 monoclonal antibody specific for the glucocorticoid-induced tumor necrosis factor receptor. Two murine tumor models were used to evaluate the therapeutic efficacies of HF10 virotherapy combined with DTA-1. The kinetics and immunological mechanisms of DTA-1 in HF10 infection were examined using flow cytometry and immunohistochemistry. Intratumoral administration of HF10 in combination with DTA-1 at a low dose resulted in a more vigorous attenuation of growth of the untreated contralateral as well as the treated tumors than treatment with either HF10 or DTA-1 alone. An accumulation of $CD8^+$ T cells, including tumor- and herpes simplex virus type-1-specific populations, and a decrease in the number of $CD4^+$ $Foxp3^+$ T regulatory cells were seen in both HF10- and DTA-1-treated tumors. Studies using Fc-digested DTA-1 and Fcγ receptor knockout mice demonstrated the direct participation of DTA-1 in regulatory T cell depletion by antibody-dependent cellular cytotoxicity primarily via macrophages. These results indicated the potential therapeutic efficacy of a glucocorticoid-induced tumor necrosis factor receptor-specific monoclonal antibody in oncolytic virotherapy at local tumor sites.