Sato et al. Journal for ImmunoTherapy of Cancer 2014, 2(Suppl 3):P58
http://www.immunotherapyofcancer.org/content/2/S3/P58

Journal for ImmunoTherapy of Cancer

POSTER PRESENTATION Open Access

Generation of interleukin-13 receptor alpha2 antigen expressing modified vaccinia ankara recombinant virus for potential cancer immunotherapy

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From Society for Immunotherapy of Cancer 29th Annual Meeting
National Harbor, MD, USA. 6-9 November 2014

Genetically modified recombinant poxviruses have shown promise in preclinical models of cancer immunotherapy due to their ability to induce effective cell-mediated immunity against target tumor-associated antigens (TAA). One such vector, recombinant Modified Vaccinia Ankara (MVA), is capable of expressing foreign genes in infected host cells. MVA is replication restricted in most mammalian cells exemplifying a unique safety profile. We have demonstrated that the interleukin-13 receptor α2 (IL-13Rα2) is selectively expressed in various solid tumors but not in normal tissues making it a promising TAA. Prophylactic and therapeutic vaccination with a plasmid vector expressing IL-13Rα2 caused only partial regression of established tumors [1], suggesting that host immune responses against IL-13Rα2 needed further enhancement. Thus, we constructed a recombinant MVA (rMVA-IL13Rα2) expressing both IL-13Rα2 and a green fluorescent protein (GFP) reporter gene. Purified virus titration by immunostaining using anti-vaccinia antibody and anti-IL-13Rα2 antibody confirmed the identity and purity of the recombinant MVA. Western Blot analysis showed the presence of IL-13Rα2 protein (65 kDa). Flow cytometric analysis of IL-13Rα2 negative T98G glioma cells infected with rMVA-IL13Rα2 virus (T98G-IL13Rα2) demonstrated surface expression of IL-13Rα2, indicating the infectivity potential of the recombinant virus. Incubation of T98G-IL13Rα2 cells with varying concentrations (0-100 ng/ml) of IL13-PE (interleukin-13 fused to truncated *Pseudomonas* exotoxin [2] resulted in depletion of GFP^+ T98G-IL13Rα2 cells in a concentration-dependent manner. Higher concentrations of IL13-PE (10-1000 ng/ml) also inhibited the protein synthesis in T98G-IL13Rα2 compared to cells infected with control pLW44-MVA. We further observed that IL13-PE treatment of rMVA-IL13Rα2 infected chicken fibroblast, DF-1 cells led to a reduction in virus titer compared to untreated cells. These results indicate that rMVA-IL13Rα2 virus can successfully infect mammalian cells and express IL-13Rα2 in a biologically active form on the cell surface. The immunization studies of rMVA-IL13Rα2 are ongoing in a syngeneic mouse model of metastatic breast carcinoma. Based on *in vitro* results, we expect the rMVA-IL13Rα2 to be a useful agent in tumor immunotherapy as a vaccine alone and in combination with other therapeutic agents to eradicate metastatic tumors.

Published: 6 November 2014

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doi:10.1186/2051-1426-2-S3-P58
Cite this article as: Sato *et al.*: Generation of interleukin-13 receptor alpha2 antigen expressing modified vaccinia ankara recombinant virus for potential cancer immunotherapy. *Journal for ImmunoTherapy of Cancer* 2014 **2**(Suppl 3):P58.

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