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Recruitment of Immune Effector Cells Against Glioblastoma-Multiforme by a MHC-Chlorotoxin Chimeric Protein

Inbal Zafir-Lavie; Or Cohen-Inbar MD, PhD; Yoram Reiter PhD; Menashe Zaaroor MD, DSc

Introduction

Glioblastoma Multiforme (GBM) is the most common malignant primary brain tumor, having a mean overall survival approaching two years. This dismal figure remains relatively stable despite tremendous progress in all areas of medicine and research. The lack of an efficient immune response against the tumor and its microinvasive nature have been attributed to its immunosuppressive capabilities and an immunosuppressing local environment. We set out to design a chimeric molecule. One end of this construct recognizes and binds tissue inducible metalloproteinase known to be induced in GBM cells (MMP-2). The other end, the effector domain, mobilizes and recruits cytotoxic T-cells to mount an effective anti-tumor reaction.

Methods

The targeting moiety is the small 36-amino acids Chlorotoxin, derived from the venom of the Israeli Yellow scorpion. The effector end is a single chain HLA-A2 (Human leukocyte antigen subtype A2) covalently bound to pp65 (phosphoprotein 65) derived from the cytomegalovirus, to which most of the human population has developed a specific immune response.

Results

The entire molecular construct was cloned and expressed in E.Coli. The protein product was isolated and purified, and then folded in vitro. Various activity assays employed demonstrated retained activity of each domain. These included flow cytometry, intracellular staining, fluorescence immunohistochemistry, radiolabeled toxicity assays etc. Initial in-vivo studies performed show great promise.

Conclusions

We present a proof of concept study for a new immunotherapy approach to battle GBM. A molecular construct which contains a non-antibody compact and highly specific targeting domain, combined with the ability to recruit anti-CMV T-cell lymphocyte population. The recruitment of potent memory CTL's to the tumor's milieu may prove resistant to the previously described local immunosuppressive environment brought about both actively and passively by the tumor.

Learning Objectives

A proof of concept study. A molecular construct for immunotherapy Against GBM.

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