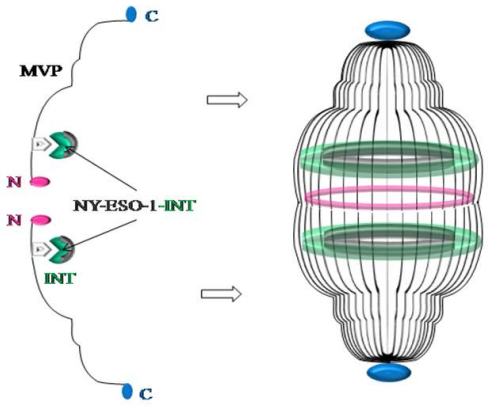
An Antigen Vault Nanoparticle Vaccine Can Effectively Stimulate Dendritic Cells and Activate a Specific T cell Immune Response

Isaac Yang MD; Yang Jian; Heather Garcia; Winward Choy BA; Daniel Tetsuji Nagasawa MD; Marko Spasic MD; Andy Trang; Horacio Soto; Kate Ericcson; Dominique Lisiero B.S.; Michelle Hickey; Carol Kruse; Robert M. Prins PhD; Leonard Rome; Linda M. Liau MD, PhD

Introduction

Glioblastoma multiforme (GBM) is the most common primary malignant brain tumor with an overall survival around 14 months. Recent studies have found that a ribonucleoprotein Vault Nanoparticle can effectively enclose an antigen and potentially stimulate the host's native immune responses against targeted tumors. In this laboratory investigation, we successfully bioengineered an antigen associated Vault Nanoparticle vaccine targeting glioblastoma and analyzed its ability to stimulate an immune response through dendritic cells and activating T cells in vitro.

Vault nanoparticle structure



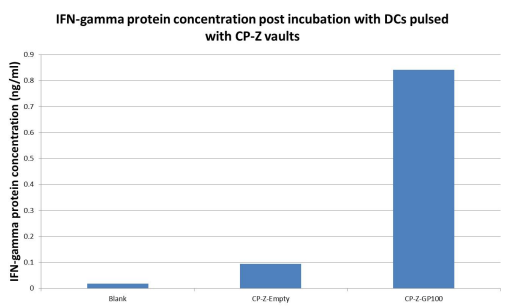
Methods

Using INT fusion proteins, GP100 (25-33) cDNA was integrated into a bioengineered CP-Z vault nanoparticle. The recombinant CP-Z-GP100 vault nanoparticle vaccine were used to immature DCs cultured from C57BL/6 mouse bone marrow. Uptake of the antigen vault nanoparticles was analyzed with fluorescent microscopy. After GP100 specific T cells were exposed to antigen vault nanoparticle treated DCs, subsequent T cell activation was assessed using an IFN-gamma ELISA assay.

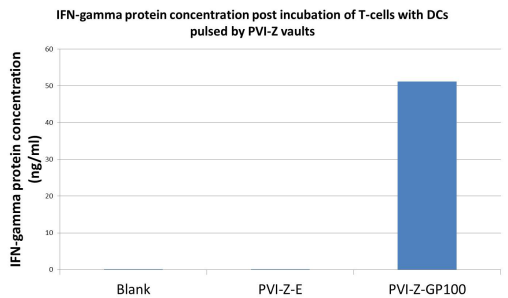
Results

Recombinant vault nanoparticles were internalized by DCs and processed for antigen presentation resulting in activated DCs. Flow cytometry demonstrated statistically significant increases in CD86, a marker for dendritic cell maturation. After treatment with the antigen nanoparticle vaccine, these DCs were then co-cultured with GP100 antigen specific T cells, and IFN-gamma levels were measured via an ELISA assay. T cells cultured with the antigen vault nanoparticle vaccine treated dendritic cells had an IFN gamma concentration that was significantly greater than either controls, the empty vaults or untreated dendritic cells (1.58 ng/mL vs. 0.07 ng/mL or 0.72 ng/mL respectively).

T-cell Activation via the CP-Z-GP100 (25-33) Nanoparticle



T-cell Activation via the PVI-Z-GP100 (25-33) Nanoparticle



Conclusions

These results demonstrate that the CP-Z and PVI-Z-GP100 (25-33) vault nanoparticles are capable of activating DCs and in turn T-cells in vitro. PVI-Z-GP100 (25-33) vaults produced a stronger response from the T-cells with an IFN-gamma concentration of 51.14ng/mL versus 0.8424ng/mL for the CP-Z-GP100 (25-33) vault. In conclusion, vault nanoparticles represent a novel delivery system for eliciting an immune response in vivo and is a promising approach to immunotherapy.

Learning Objectives

Assess the potential use of vault nanoparticle vaccine against brain cancer.

Future Directions

Characterization of the in vivo mechanism of the immune response to CP-Z and PVI-Z-GP100 (25-33) vault nanoparticles in tumor-bearing mice.

We hypothesize that these nanoparticles may induce an immune response in the Pmel-1 syngeneic mouse model following in vivo vault injection.

Establish a preclinical understanding of the feasibility and potential of bioengineered vault nanoparticle vaccines as a novel mechanism to optimize immunotherapy delivery for the treatment brain cancer.

Institution

UCLA - Department of Neurosurgery