Glioblastoma Derived Exosomes Induce Apoptosis in Cytotoxic T cells Through a Fas Ligand Mediated Mechanism

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Introduction

Glioblastoma multiforme deploys a number of weapons to thwart the immune system. Within the tumor microenvironment, tumor infiltrating T cells fall victim to cellular and soluble mediators of apoptosis. In prostate and colorectal cancer models, exosomes can induce T cell apoptosis. Exosomes are tiny, membrane bound vesicles that are released from a cell. They contain functional mRNA and protein and have cell surface molecules representative of their parent cell. It is not known if GBM derived exosomes can also mediate apoptosis. In this study, the role of GBM derived exosomes in T cell apoptosis is explored.

Methods

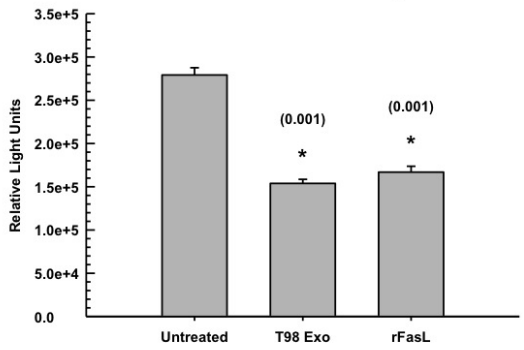
Exosomes are isolated from the T98 human malignant glioma cell line using differential ultracentrifugation. GBM derived exosomes or recombinant Fas ligand (FasL) are co-cultured with Jurkat A3 T cells. T cell viability is then quantified and apoptosis is measured using caspase-8 and caspase-3 luminescent assays.

Results

T98 derived exosomes and recombinant Fas ligand significantly decrease T cell viability. (Figure 1) Significant caspase-8 activation is seen in T cells co-cultured with T98 derived exosomes and recombinant FasL. (Figure 2) Significant caspase-3 activation is also seen when T cells are co-cultured with T98 derived exosomes. (Figure 3).

Figure 1

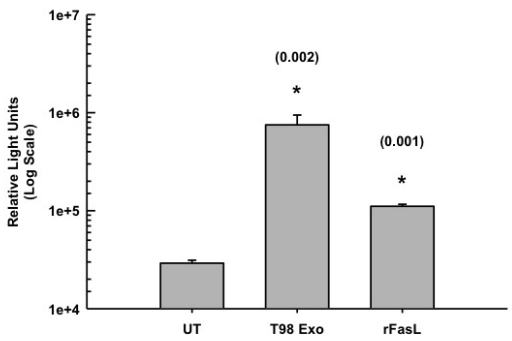
T98G exosomes reduce Jurkat T cell viability



* Indicates significance

Figure 2

Induction of caspase-8 activity by GBM-derived exosomes



* Indicates significance

Conclusions

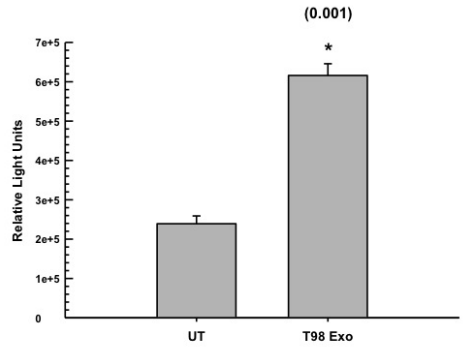
GBM derived exosomes induce T cell apoptosis. The mechanism(s) by which exosomes do this is under investigation. This method of immune suppression has not previously been described with glioblastoma multiforme. This research opens new avenues to antagonize GBM related immune system malfunction.

Learning Objectives

At the conclusion of this session, participants will be able to: 1) describe the origin and function of exosomes, 2) discuss the mechanisms of T cell inhibition in GBM, and 3) describe how GBM derived exosomes affect T cells in both the tumor microenvironment and systemically.

Figure 3

Induction of caspase-3 activity by GBM-derived exosomes



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