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

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Abstract

INTRODUCTION: Glioblastoma multiforme deploys a number of weapons to thwart the immune system. Within the tumor microenvironment, cytotoxic T cells fall victim to Fas ligand (FasL) induced apoptosis. In prostate and colorectal cancer, exosomes can mediate this FasL induced 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 FasL triggered apoptosis. In this study, the role of tumor derived exosomes as the delivery vehicle for FasL is explored.

METHODS: Exosomes are isolated from the T98 cell line using differential ultracentrifugation. FasL expression in the cell line and derived exosomes is determined using reverse transcription polymerase chain reaction (RT-PCR) and Western blotting. GBM derived exosomes, recombinant FasL, and exosomes treated with an anti-FasL antibody are co-cultured with Jurkat A3 T cells. Apoptosis is measured using a caspase-8 luminescent assay.

RESULTS: FasL is expressed by the T98 cell line and is present on the surface of the cells and their exosomes (Figure 1). Caspase-8 activation is seen in T cells treated with GBM derived exosomes and recombinant FasL, but not with exosomes treated with anti-FasL antibody or exosome free supernatant (Figure 2).

CONCLUSION: GBM derived exosomes induce T cell apoptosis through a FasL mediated mechanism. This method of immune suppression has not previously been described. This research opens new avenues to antagonize GBM related immune system malfunction.