309 PROTEIN KINASE C IS AN UPSTREAM REGULATOR OF IL13RA2 AND SMALL MOLECULAR ACTIVATOR ENHANCES CAR T MEDIATED KILLING

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Background Glioblastoma multiforme (GBM) is the most aggressive primary malignant brain cancer with a median survival of 16–20 months. Maximal safe resection and adjuvant chemotherapy improve survival but there is no cure and hence improved therapies are urgently needed. CAR T cell therapy has been FDA approved for hematologic malignancies but there are some barriers to their application for solid tumors in the clinic such as heterogenous tumor antigen expression. Chimeric Antigen Receptor (CAR) T Cells combine the cytolytic potency of T cells with the tumor specificity of an antibody. The interleukin 13 receptor alpha 2 (IL13Ra2) is an important target of CAR T cell therapy in ongoing GBM clinical trials. However, regulation of IL13Ra2 expression in GBM is unclear. Identifying upstream regulators of IL13Ra2 will not only help delineate IL13Ra2 carcinogenesis but also may help improve CAR T cell therapy.

Methods Utilizing knockout and overexpression constructs, we have identified protein kinase C family as an upstream regulator of IL13Ra2 transcription and translation in GBM cell lines by performing western blots. We have also identified a small molecule regulator of IL13Ra2, Ingenol-3-Angelate (I3A), that inhibits U87 tumor cell proliferation.

Results I3A enhances IL13Ra2 re-directed CAR T cell mediated tumor cytolysis *in vitro*. Importantly, I3A treatment increases interferon gamma secretion by T cells.

Conclusions Taken together, our data implicates PKC isoforms as an upstream regulator of IL13Ra2. I3A treatment may serve as a therapeutic strategy to enhance CAR T mediated killing.

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