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MET-targeting CAR T cells enhance tumor cell killing and cytokines release in glioma models when combined with radiation therapy

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Glioblastoma (GBM) is the most frequent primary brain tumor with dismal prognosis after radiation therapy, a standard treatment option for this disease. Recently, RT has been investigated as a mediator of effects of T cell-based therapies in the context of immunosuppressive GBM microenvironment. The MET receptor is an oncogene involved in radiation resistance, and stem-like properties of GBM. We study the impact of MET-targeting chimeric antigen receptor (CAR) T cells (MET-CAR T cells) combined with radiation in GBM, and hypothesize that this combination acts synergistically in terms of tumor growth control.
We co-cultured MET-CAR T cells with adherent (2D) and stem-like (3D) human GBM cells with or without RT and assessed the killing efficiency and cytokine production of CAR T cells. Our results indicate that 5Gy radiation combined with MET-CAR T cells increases their potential in tumor cell killing. We observed increased CAR T cells effect at lower CAR T to target cells ratios when combined with radiation, even when radiation treatment alone did not lead to a significant decrease in GBM cell viability. This phenomenon was similar in both types of cell lines as well as across different levels of MET expression, and different sensitivity to CAR T cells. The mechanisms behind this observation were investigated via intracellular cytokine measurements. The most prominent response was in TNF-alpha expression. Increase in Granzyme B expression was observed in co-culture with some of the GBM cell lines and was more prominent in CD8+ subpopulation of CAR T cells. Increase in IFN-gamma was observed in some adherent glioma cell lines but was absent in co-culture with stem-like glioma cell lines. Our pilot in vivo study in orthotopic GBM model demonstrated tumor reduction after 48h of intravenous and intracranial injection of MET-CAR T cells. The RT-CAR T combination studies are to follow.
In conclusion, our data demonstrates the potency of MET-CAR T cells against GBM, and increased efficiency when combined with radiation. The suggested mechanism is the increased activation of T cells in TNF-alpha-dependent-manner.

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