CHEMOTHERAPY RESISTANT GAMMA DELTA T-CELL IMMUNOTHERAPY CAN LEVERAGE SYNERGISTIC LIGAND EXPRESSION THROUGH COMBINATIONAL CHEMOTHERAPY AND PARP-INHIBITOR USE TO ENHANCE TUMOR CELL RECOGNITION & KILLING

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Background Cellular Immunotherapies, which have been transformative in the treatment of liquid tumors, have had extremely limited efficacy in solid tumors to-date, in part due to the challenges of efficiently targeting the tumor heterogeneity. Gamma-delta T cells recognize and immediately respond to stress-induced Natural Killer Group D Ligands (NKG2DL) which can thereby differentiate between healthy and malignant tissue. We designed methylguanine-DNA methyltransferase (MGMT) expressing gamma-delta T cells engineered to be TMZ resistant (DeltEx Drug Resistant Immunotherapy or DRI) which can be administered concurrently with alkylating chemotherapy. This leverages the brief but substantial upregulation of NKG2DL from the pharmacokinetic activity of the chemotherapy. We and others have shown checkpoint inhibitors improve gamma-delta T cell function and can be combined with chemotherapy to target checkpoint mediated tumor cell escape. Further, this approach can be used with DNA damage response (DDR) inhibitors, such as PARP-inhibitors or ATM kinase inhibitors to enhance the upregulation of NKG2DL and amplify the chemotherapy-induced vulnerability of tumor cells.

Methods Glioblastoma cells isolated from patient derived xenografts (PDX) were used to determine if TMZ and blood brain barrier penetrant DDR inhibitors could enhance NKG2DL ligands. Three PDX with distinct subtypes and genetic profiles were utilized. GBM PDX-derived cells were propagated with epidermal growth factor (EGF) and fibroblast growth factor (FGF) but without serum to best model parental tumors in vitro. Quantitative real-time PCR was used to determine expression of a panel of NKG2DL under hypoxic and normoxic conditions

Results We found a heterogeneous induction of NKG2DL expression with the combination of niraparib + TMZ. While the combinatorial treatment induced stress responses in all cells tested, the specific mRNAs induced, the extent of induction, and the effect of hypoxia varied. Niraparib and TMZ induced >10-fold induction of MICA and MICB in GBM456 cells or ULBP1 in GBM39 cells. The cell type specific inductions of these three targets were reduced by hypoxia and low glucose conditions, suggesting microenvironmental regulation will be important in vivo.

Conclusions This approach holds promise for solid tumor treatment leveraging the ability of the gamma-delta T cells complex polyclonal receptor repertoire to identify and kill tumor cells with combinational therapeutic treatment to drive increases in NKG2DL. The broad utility of alkylating chemotherapies in solid tumor treatment, suggests that this mechanism could be applicable across multiple indications to drive tumor cell immunogenicity in combination with DeltEx DRI cells to increase cytotoxicity and tumor cell killing.

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