A NOVEL DENDRITIC CELL VACCINE UTILIZING MANNAN ANCHORED TO IRRADIATED TUMOR CELLS IN THE PRESENCE OF IMMUNE ADJUVANTS

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Background While the past decades have seen an explosion of innovation in immunotherapies, most have failed in their clinical studies. One of the barriers encountered across these trials is that despite demonstrated cytotoxicity, tumor immune evasion renders these treatments ineffective.

Glioblastoma (GBM) is one of these tumors where experimental immunotherapeutics have continued to fail. The median survival of GBM remains at 15 months with the primary treatment being surgical resection, radiation, and chemotherapeutic over the past decade. To breach this stalemate, we require new therapeutics that both can target tumor immune evasion and can balance efficacy with toxicity.

Our lab previously developed a subcutaneous autologous tumor vaccine utilizing a phagocytosis-stimulating ligand mannan anchored to irradiated (IR) tumor cells with the adjuvants toll-like receptor (TLR) agonists and immunostimulant anti-CD40 antibody (collectively abbreviated as MBTA). This regime allowed recognition of tumors resulting in a coordinated innate and adaptive immune response in both prophylactic and therapeutic studies with colon carcinoma, breast tumor, and GBM mouse models. The aim of our study was to generate a dendritic cell (DC) vaccine utilizing this strategy.

Methods To assess if MBTA anchored GBM cells could mature DCs in-vitro, we harvested bone-marrow DCs (BMDCs) from mice and co-cultured them with MBTA GBM cells for 24 hours. Analysis was performed by flow cytometry and ELISA to confirm maturation markers and DC phenotype.

Results We found robust up-regulation of co-stimulatory molecules CD40, CD80 and CD86 and preferential upregulation of MHCI in the MBTA group with ELISA analysis demonstrating MBTA DCs significantly upregulated Type 1 cytokines (TNFa and IL-6) and limited regulatory cytokine (IL-10) secretion across GBM cell lines.

Mice vaccinated with MBTA DCs had a significant decrease in lung metastasis compared to controls with lung immunohistochemistry demonstrating robust perivascular lymphocytic infiltration. Currently, we are working on demonstrating this efficacy in a glioblastoma model.

Conclusions Collectively our results demonstrate that MBTA is an effective strategy to mature and load tumor antigens onto DCs ex-vivo. It has efficacy as a DC vaccine to prevent melanoma metastasis and potential as a glioblastoma DC vaccine.

Acknowledgements The authors acknowledge the NCI-CCR affiliated staff for their assistance with animal housing and the NCI CCR Flow Cytometry Core Members for their expertise in flow cytometry.

Ethics Approval The National Cancer Institute (NCI) Animal Use and Care Committees approved the present study under NOB-010 and NOB-016.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0425