REHEATING THE GLIOBLASTOMA TUMOR MICROENVIRONMENT BY DIRECT CONVERSION OF GLIOBLASTOMA TO INDUCED DENDRITIC CELL-LIKE ANTIGEN PRESENTING CELLS

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Background Although cancer immunotherapy has revolutionized treatment for many solid tumors, its efficacy is limited in GBM due in large part to the ‘cold’ tumor microenvironment (TME) of the GBM tumor that lacks critical immune cells like dendritic cells (DC) and T cells but instead is enriched in immunosuppressive cells. New approaches are necessary to overcome these challenges. The lack of intratumor DCs may be partly due to circulating DCs unable to traverse physical barriers in non-immunogenic tumors, the blood-brain barrier in GBM. We propose a shift in the scientific and treatment paradigm of cancer immunotherapy, calling for tumor cells to take on a central, active role in initiating their own immunity right in the TME.

Methods Using NETZEN, an integrated deep-learning, and gene network-based ranking computational platform, we identified cell fate determinants (CFDs) to convert GBM cells directly into induced dendritic cells (iDC) inside the TME. CFDs were delivered using a viral vector, and conversion was assessed by immunophenotyping, scRNA-seq. iDCs were functionally validated by their ability to efficiently cross-present exogenous antigens to naive CD8 T cells, a critical hallmark of natural DCs, and activate tumor-specific T cells to kill GBM cells in a cytotoxicity assay.

Results A four-CFD subnetwork anchored by PU.1 was sufficient to convert mouse GBM cells to iDCs (CD45+MHCII+CD80/86+MHCI+). iDCs are growth arrested, exhibit 3-fold higher phagocytic activity, and upregulate the canonical antigen processing and presenting machinery by 10–40-fold, resulting in 100-fold greater efficiency at processing ovalbumin and cross-presenting SIINFEKL to naive OTI-CD8+ cytotoxic T lymphocytes (CTL). In addition, iDCs efficiently cross-present exogenous antigens to naive CD8+ CTLs and elicit >30-fold higher activation and cytotoxicity in tumor-specific T cells than in native GBM cells, confirming their DC-like properties. Lastly, intratumoral GBM-DC conversion in a syngeneic orthotopic GBM model resulted in a significant reduction in tumor burden and an increase in survival compared to controls (Log-rank, p=0.01) with synergistic efficacy with classical DC-based tumor vaccination and potentially with ICIs.

Conclusions GBM-derived iDCs acquired DC-like functions and could elicit robust intratumor immune activation, thereby overcoming many current limitations of immunotherapy in GBM. We aim to develop a low-cost, off-the-shelf gene therapy-based fate conversion tumor immunotherapy.

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REFERENCES