

DIVERGENT MECHANISMS OF DENDRITIC CELL DYSFUNCTION IN PRIMARY AND ADOPTIVE CELLULAR THERAPY-ESCAPED GLIOMAS

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Background Dendritic cell (DC) plays crucial role in eliciting anti-tumor immune response through both innate and adaptive immune system. Our group has developed an adoptive cellular therapy (ACT) against high grade gliomas, which significantly improves survival in murine models of CNS malignancies. Our studies have shown that the efficacy is associated with the observed increase in intratumoral dendritic cells (DC) which arise from transferred hematopoietic stem cells (HSC).¹ However, tumors develop diverse mechanisms to restrict DC function to evade immune surveillance. In this study, we will address the various DC dysfunctional mechanism in both primary and ACT escaped tumors.

Methods ACT treatment was administered to mice bearing the KR158B glioblastoma cell line to get ACT escaped tumor. The mice received 9 Gy of irradiation prior to the transfer of hematopoietic stem cells and tumor-reactive T cells, followed by three doses of BMDC vaccine. Tumor associated DCs sorted from primary and ACT escaped tumors were subjected to assess DC function or gene expression profiling. T cell proliferation, T cell activation markers, and IFN γ secretion were measured by flow cytometry and ELISA as a readout for DC-T cell co-culture functional assays. Brain tumor slices were prepared using a vibratome, and the conditioned medium from the slice culture was used to pre-treat DCs to determine the impact of brain tumor secretion on DCs.

Results Functional evidence demonstrated that DCs from ACT-escaped tumors is impaired in activating tumor-reactive T cells. By comparing the gene expressing profiles between tumor associated DCs in primary and ACT escaped tumors, we found a significant decrease in cDC marker genes, antigen assembly genes, and MHC molecules in ACT-escaped tumor DCs, compared to primary tumor DCs, suggesting a decreased cDC population and impaired antigen presentation in ACT-escaped tumor DCs. To determine whether secreted factors from tumor microenvironment that drives DC dysfunction, conditioned medium (CM) from tumor brain slices were tested in inducing DC dysfunction in vitro. CM from primary tumor brain slices suppressed DC function compared to healthy brain slice CM. Further results showed that non-tumor cell-derived secretion from the slices drives DC dysfunction in primary tumors. Strikingly, unlike primary tumor brain CM, ACT-escaped tumor brain slice CM did not decrease DC function capacity, suggesting different tumor-driven DC dysfunctional mechanisms in primary and ACT-escaped tumors.

Conclusions The primary glioma tumor drives DC dysfunction through non-tumor cell-derived secretion, whereas the ACT-escaped tumor employs a different mechanism involving cDC exclusion and impaired MHC expression and antigen loading.

REFERENCES

1. Wildes TJ, et al. Cross-talk between T Cells and Hematopoietic Stem Cells during Adoptive Cellular Therapy for Malignant Glioma. *Clin Cancer Res*, 2018; **24**(16): 3955–3966.

Ethics Approval The study is approved by the University of Florida Institutional Animal Care and Use Committee (IACUC) and are covered under protocol number

IACUC20210000053. All participants were given informed consent before taking part.

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