GLUTAMINE BLOCKADE AND ANTI-PD1 TREATMENT REPROGRAMS THE TUMOR INFILTRATING MYELOID CELLS IN MOUSE MODEL OF SOFT TISSUE SARCOMAS

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Background Immunotherapy holds great potential to treat cancers such as sarcomas. A major impediment for immune-mediated tumor killing in sarcomas is a strong presence of suppressive cell types such as Myeloid Derived Suppressor Cells (MDSC) dominating the Tumor Immune Micro-Environment (TIME) and a dearth of effector cell types such as T Cells. Cellular metabolism has emerged as a novel checkpoint to modulate immune responses by targeting various metabolic pathways. Glutamine is a key metabolite participating in the TCA cycle and is implicated in sarcoma genesis and its blockade has shown to skew immune cell function and phenotype. We used JHU083, a novel produg of a glutamine antagonist (6-Diazoo-5-oxo-L-norleucine) to rid the TME of glutamine and interrogate its downstream effects on the TIME.

Methods Cells derived from primary tumors from LSL-KrasG12D/+; p53flox/flox mice (KP Cells) were subcutaneously injected in C57BL/6j mice. The mice were treated with JHU083 (1mg/kg on days 7–11 and 0.3mg/kg daily till end) and anti-PD1 monoclonal antibody (100ug on days 7, 9, 11 and 13) or saline and euthanized at Day 20. We studied the 3 major tumor infiltrating myeloid cell populations: Monocytic MDSC, Granulocytic MDSC (GMDSC) and Macrophages by flow cytometry and FACS sorted them to profile their transcriptome using NanoString Mouse Myeloid Innate Immunity Panel.

Results The combination treated group had significantly less tumor burden at the end of Day 20 than the control group. We saw a significant reduction in the percentage of GMDSC in the combination treated group. We observed a consistent reduction in expression of Csf3 and Csf3r and an upregulation of complement related genes specifically C1qa, C1qb and C1qc across the three subsets in the treated group. Transcriptionally, the most affected cell type was the GMDSC subset which saw an upregulation of Apoe and other genes such as Acly, Calr, Pf4, Grm, Trem2 upon glutamine blockade. These genes are known to be expressed in a subset of myeloid cells in multiple human cancers.

Conclusions Combination of glutamine blockade and anti-PD1 therapy can be an effective strategy to modulate myeloid cell frequency and phenotype in this model of soft tissue sarcoma. Transcriptional changes upon glutamine blockade, especially upregulation of Apoe, a key apolipoprotein implicated in cholesterol transport points towards rewiring of metabolism of the myeloid cells. This hints that the heterogenous metabolome/lipidome might hold clues to the differential responses to glutamine blockade in the myeloid subsets.

REFERENCES

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