GLUTAMINE BLOCKADE IN COMBINATION WITH IMMUNE CHECKPOINT BLOCKADE REMODELS THE MYELOID LANDSCAPE IN MOUSE MODELS OF SOFT TISSUE SARCOMAS

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Background Immunotherapy holds great potential to treat cancers such as sarcomas for which the clinical outcomes using conventional therapies haven’t changed much in decades. A major impediment for immune mediated tumor killing in sarcomas is a strong presence of immunosuppressive 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 [1]. Cellular metabolism has emerged as a novel immune-checkpoint to modulate the immune responses by targeting various metabolic pathways. Glutamine is a key metabolite participating in the TCA cycle and is implicated in sarcoma-genesis [2] and its blockade has shown to skew immune cell function and phenotype [3]. We used JHU083, a novel prodrug of a glutamine antagonist (6-Diazo-5-oxo-L-norleucine) to rid the TME of glutamine and interrogate its downstream effects on the TIME.

Methods We employed a transplantable mouse model of soft tissue sarcomas [4]: Cells derived from primary tumors from LSL-KrasG12D/+ p53flox/flox mice (KP Cells). Wild-type C57BL/6J mice were subcutaneously injected with 200,000 KP cells. They were treated with JHU083 (1mg/kg on days 7–11 and 0.3mg/kg till end) and anti-PD1 monoclonal antibody (100ug on days 7, 9, 11 and 13) or vehicle control and isotype control. On Day 22, the mice were sacrificed, and the tumors were harvested and interrogated using flow cytometry and Immuno-histochemistry (IHC) to reveal the effects of different treatment groups on the immune landscape.

Results The combination treated group had significantly less tumor burden at the end of Day 21 than the control group (Figure 1). Although the myeloid cells outnumbered the lymphocytes across both the groups, the percentage of G-MDSCs reduced significantly in the combination treated group (17% in the combination, vs 29% in the control, p=0.058, Figure 2). The density of T cells and B cells infiltrating the tumors was also higher for the combination treated group than other groups as measured by IHC (Figure 3).

Conclusions Our data suggests that blocking glutamine with anti-PD1 therapy leads to a change in the proportion of myeloid cells in the TIME. The combination treatment increased the influx of T and B cells while reducing the density of the...
immunosuppressive G-MDSCs. For cancers with immune excluded/desert phenotypes this therapy has the potential to make the tumors amenable to immunotherapy leading to better clinical outcomes. Further transcriptomic and metabolomic studies will reveal the mechanistic pathways by which glutamine blockade is able to remodel the myeloid landscape.

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Ethics Approval All animal procedures performed were approved by the Johns Hopkins University Animal Care Committee.

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