TARGETING TIM-3 ON T REGULATORY CELLS MAKE NONRESPONSIVE COLD MELANOMA, MORE RESPONSIVE TO IMMUNE MEDIATED TUMOR CONTROL

Hridesh Banerjee*, Hector Rosado, Benjamin Murter, Lawrence Kane. University of Pittsburgh, Pittsburgh, PA, United States; UPMC Medical School, Pittsburgh, PA, United States

Background: Cold Tumor mouse model study are useful, as a few category of human tumor in breast, brain, prostate, pancreas and ovary are Cold and resistant to Immune checkpoint inhibitors (ICIs) based therapeutic treatments. one of the widely studied model in mouse for cold tumor is B16F10 melanoma, and this model is known to be non-responsive to checkpoint inhibitor therapy. while T regulatory cells have been known to play a major role in cancer immunosupresion, targeting T reg cells directly has been a challenge, due to their role in immune homeostasis. we use TIM-3 expressing Tregulatory cells as a significant proportion of Treg cells in various mouse and human tumor model are known to be expressing TIM-3 and this expression is far restricted to the site of Tumor.

Methods: C57BL 6 mice were injected with Tumor cells subcutaneously, followed by tracking of Size of tumors and also immuno typing of tumor and lymphoid organ. for Treg specific targeting TIM-3 conditional Knockout mouse were generated and Bred to FoxP3 ERT2 Cre model to induce time dependent knocking out of T regulatory cellTIM-3. efficiency of Knock out in various organ and tumor was confirmed by Flow cytometry.

Results: MC38(immune responsive) and B16F10( non immune responsive), tumors are both delayed in progression of tumor when Treg cells are incapable of inducing TIM-3.

Frequency of Tregulatory cells goes down in tumors of TIM-3 conditional knockout mouse.

CD8 exhaustion kinetics in TIM-3 Knockout mouse is delayed and knockout mouse survive longer after tumor induction.

Delay in B16F10 melanoma may be a indicative of better immune response in TIM-3 Knockout mice.

Conclusions: Targeting TIM-3 in Combination therapy, with their Role in Treg specificity may be a viable and effective strategy. Inability of Treg cells to persist in tumors in absence of TIM-3, indicate to the fact that TIM-3 may be playing a role in survival of Treg cells in tumor microenvironment, and a possibility of role of TIM-3 in T reg cells traffic in tumors can also be not ruled out.

surprisingly along with our previously published Data on MC38 where we have shown that T cell exhaustion kinetics gets delayed , we see the same trend in cold tumor model, B16 F10. suggestive of a possibility of these tumor being more responsive to immune therapy.

REFERENCES: