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LAG3 BLOCKADE IN COMBINATION WITH GITR IMPROVES ANTI-TUMOR IMMUNE RESPONSES IN A PRECLINICAL MELANOMA MODEL

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Background Immune checkpoint blockade (ICB) therapies anti-PD1 and anti CTLA-4 have had tremendous successes in clinic. However, many patients are either inherently resistant or acquire resistance to these therapies. Appropriately activating co-stimulation pathways of T cells together with blocking immune checkpoints can provide substantial anti-tumor responses. Glucocorticoid induced TNFR Related protein (GITR), is a costimulatory molecule whose engagement with agonist antibodies leads to proliferation, cytokine production and survival of cytotoxic T cells, and destabilization and depletion of suppressive T regulatory cells in the tumor microenvironment, making it an attractive target for cancer immunotherapy. GITR agonism as a monotherapy in murine models of advanced melanoma leads to increased effector T cell dysfunction with a marked upregulation in expression of exhaustion markers PD-1 and Lag3, making them rational targets to combine with GITR agonism.

Methods C57BL/6 mice were implanted with B16-F10 melanoma and were treated with a single dose of GITR Agonism with or without anti Lag3 on Day 7 post tumor implant, followed by anti Lag3 every 3 days. Spectral flow cytometry and immunohistochemistry was used to study immune cell repertoires. Splenic B cell repertoire was studied using BCR IgH sequencing.

Results We show that combining GITR agonism with Lag3 ICB therapy, leads to better tumor control, and improved survival in mice with advanced ICB resistant B16 melanoma. Additionally, mice treated with GITR agonism monotherapy show a marked increase in activated B cells infiltrating the tumor microenvironment. This infiltration is further increased when GITR agonism is combined with Lag3 blockade therapy. These tumor-infiltrating B cells are highly activated with an increased expression of activation markers CD86, MHC-II, and CD38. The spleens from mice treated with GITR agonism in combination with Lag3 blockade demonstrate increased hyperplasia, and an increase in size and number of germinal centers. B cell receptor sequencing from the spleens of these mice revealed an increased clonality and reduced entropy in mice treated with GITR agonism + Lag3 blockade therapy.

Conclusions Increased B cell activity observed in these mice warrants further investigation into the role and mechanism of action of a GITR/Lag3 combination therapy. Our results suggest that combining GITR agonism with Lag3 blockade is a safe and potent therapeutic strategy to overcome ICB resistance in mice with advanced melanoma.

Ethics Approval This study was approved by the Institutional Animal Care and Use Committee (IACUC) and Memorial Sloan Kettering Cancer Center

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