Background Immune checkpoint inhibitors (ICIs) can overcome the ability of tumor cells to evade the immune system. However, current FDA-approved ICIs have been unsuccessful in treating relapsed medulloblastoma. The absence of traditional mediators of immune evasion combined with the paucity of lymphocytic infiltrates highlights the importance of exploring alternative immune checkpoints on myeloid cells, the most abundant infiltrating immune cell in medulloblastoma. One promising target is V-domain Ig Suppressor of T-cell Activation (VISTA), a predominantly myeloid, inhibitory immune checkpoint that has been implicated in suppressing T-cell activation and reprogramming myeloid cells towards an anti-inflammatory pro-tumoral state. Thus, we hypothesize that myeloid cells, particularly tumor-associated macrophages, use VISTA to promote an immunosuppressive tumor microenvironment in medulloblastoma.

Methods Here, we utilized an established syngeneic murine mouse model of medulloblastoma that faithfully recapitulates recurrent/refractory human disease. Harvested tumors were dissociated, enriched for immune cells, and analyzed by flow cytometry. Expression of VISTA on tumor-associated macrophages and T-cells was correlated to the immune phenotype of the tumor, as determined by the ratio of T-effector (Teff) to inhibitory T-regulatory cells (Tregs). Immunohistochemical staining of murine tumors for VISTA was also performed.

Results Flow cytometry analysis revealed an abundance of CD11b+ myeloid cells compared to CD3+ lymphoid cells. Within the CD3+ lymphoid compartment, there was a significantly higher percentage of CD4+ T-cells (mean=52.3%) compared to CD8+ T-cells (mean=2.72%) (n=6, p<0.05). Of note, a significant percentage of these CD4+ T-cells were CD4+ Tregs (mean=18.5%). Furthermore, expression of VISTA was evaluated across CD45hiCD11bhi macrophage-like cells, CD45intCD11binh microglia-like cells, and CD4+ FoxP3+ Tregs. Our findings were able to identify strong expression of VISTA across all three infiltrating immune populations, with a significantly higher average MFI on the CD45hiCD11bhi macrophage-like cells (n=9, p<0.05). Furthermore, immunohistochemical staining of murine medulloblastoma tumors revealed notably more VISTA+ cells within the tumor relative to the adjacent cerebellar tissue.

Conclusions Ultimately, this study explores the immunomodulatory role and therapeutic potential that VISTA plays in medulloblastoma. The enriched expression of VISTA on myeloid cells and Tregs within the tumor correlates with a low ratio of Teff:Tregs, suggesting that VISTA may be a key mediator of the ‘cold’ tumor microenvironment. Future studies aim to identify expression of VISTA within myeloid subpopulations and whether blocking VISTA is sufficient to reverse immune suppression in this model.

REFERENCES

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