Immune dependency of the anti-VEGF treatment effect against glioma

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The majority of glioblastoma patients receive corticosteroids at some point during the course of the disease to treat brain edema. Since steroids are immunosuppressive, immunotherapy trials increasingly aim to avoid the use of steroids and consider bevacizumab, an anti-VEGF antibody which also alleviates edema, as alternative. Targeting VEGF in the context of immunotherapy may additionally have immune stimulatory effects, as VEGF is also a potent immunosuppressive factor. We explored the immunomodulatory mechanisms of anti-VEGF treatment in comparison with dexamethasone in gliomas.

Treatment with an anti-murine-VEGF antibody (B20) prolonged the survival of immunocompetent wildtype mice ($p < 0.0001$) but not of immunodeficient Pfp/Rag2 KO mice, indicating that the immune system is essential for the effect of the anti-VEGF treatment. At an early timepoint when IgG controls and dexamethasone-treated mice became symptomatic, B20-treated tumors showed increased infiltration with T cells and myeloid cells, and decreased vessel density, while B20 tumors at the survival endpoint resembled IgG-controls, indicating treatment resistance. Gene expression in FACS-sorted tumor cells from B20-treated mice was dominated by hypoxia, neural development, invasion, TGF-β, Notch and Wnt signatures as well as concerted upregulation of Kmt2 H3K4 methyltransferases. In CD11b+ myeloid cells sorted from B20 tumors, M1 hallmark genes and T cell activation genes were upregulated, while M2 genes were downregulated. Deconvolution revealed a transient shift towards pro-immune microglia/macrophages as well as increased NK cells and DCs. In CD8+ and CD4+ T cells, B20 increased the expression of S1pr1 and of α/β TCR genes, consistent with oligoclonal expansion. The proportion of progenitor-like exhausted CD8+ cells, which can be reinvigorated by PD-1 blockade, was increased in B20-treated tumors. Among CD4+ T cells, B20 caused skewing towards the CD4+ T_{FH} cell lineage, while dexamethasone increased expression of T_H2 cytokines. Immune cell depletion in B20-treated animals demonstrated that CD8+ and CD4+ T cells but not NK cells were necessary for the survival-prolonging effect of anti-VEGF treatment. In human glioblastoma patients, high Vegfa expression was associated with decreased immune cell infiltration and immunosuppression. By spatial transcriptomic analysis, a strong negative association between regional Vegfa expression and T cell abundance was found in glioblastoma tissue.

In conclusion, anti-VEGF therapy has significant immunostimulatory effects, mediated by CD8+ and CD4+ T cells as well as pro-immune modulation of the myeloid compartment. However, pro-immune effects are largely transient, so that an early treatment window of opportunity may exist during which anti-VEGF treatment in combination with an effective immunotherapy could have a substantial supportive effect, extending beyond its anti-edema and anti-angiogenic activity.