PP2AC deficiency enhances tumor immunogenicity by activating STING-type I interferon signaling in glioblastoma

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Background Glioblastoma (GBM) is an immunologically ‘cold’ tumor that does not respond to current immunotherapy. Low immunogenicity of GBM with minimal MHC-I expression and paucity of T cell infiltration are major barriers for effective immune checkpoint blockade (ICB).1–4 PP2A is a major protein phosphatase that account for 50% to 70% of the total serine/threonine phosphatase activity.5–6 Our group was the first to report that pharmacological inhibition of the PP2A catalytic subunit (PP2Ac) enhances the efficacy of ICB in multiple PD-1-resistant mouse tumor models.7,8 However, given the ubiquity of PP2A expression in many cell types and the mechanisms of how PP2A regulates anti-tumor immunity is unclear.

Methods We used in vivo orthotopic glioma ‘cold’ tumor SB28 model, which has shown to mimic the feature of human glioma patients with low mutational burden, few T cells infiltration and non responsive to immune checkpoint blockades. We also used single cell RNAseq technology and flow cytometry to analyze the immune cell components in glioma microenvironment. We also established glioma-dendritic cells (DCs)-T cells co-culture assay for antigen presentation. In addition, we used RNAseq, CRISPR KO, biochemical assays such as co-IP, to identify the downstream signaling pathway and underlying mechanisms. In summary, we used a variety of methods including human patient samples, mouse models, scRNAseq, FACS, cellular, molecular and biochemical assays.

Results We demonstrate a fundamental role for the α isoform of the catalytic subunit of protein phosphatase-2A (PP2Ac), in regulating glioma immunogenicity. Genetic ablation of PP2Ac in glioma cells enhanced double stranded DNA (dsDNA) production and cGAS-type I interferon (IFN) signaling, MHC-I expression, and tumor mutational burden. In co-culture experiments, PP2Ac deficiency in glioma cells promoted dendritic cell (DC) cross presentation and clonal expansion of CD8+ T cells. In vivo, PP2Ac depletion sensitized tumors to immune checkpoint blockade and radiotherapy treatment. Single cell analysis demonstrated that PP2Ac deficiency increased CD8+ T cell, NK cell, and DC accumulation and reduced immunosuppressive tumor associated macrophages. Furthermore, loss of PP2Ac increased IFN signaling in myeloid and tumor cells and reduced expression of a tumor gene signature associated with worse patient survival in TCGA.

Conclusions Collectively, this study establishes a novel role for PP2Ac in inhibiting dsDNA-cGAS-STING signaling to suppress anti-tumor immunity in glioma. Our study also provides the clinical insight to initiate a new clinical trial of local delivery of PP2Ac inhibitor LB100 with ICB for glioma patients.

REFERENCES

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