

Modulating EETs to reprogram glioblastoma toward a pro-resolution phenotype

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Introduction. Glioblastoma (GBM) is characterized by an immune-rich tumor microenvironments with macrophages/microglia comprising up to 70% of the tumor mass. However, endogenous pathways that actively resolve inflammation remain poorly understood in GBM. Despite a median overall survival of only 12-15 months, therapeutic strategies targeting inflammation resolution in GBM have received little attention. Epoxyeicosatrienoic acids (EETs) are endogenous bioactive lipid mediators with anti-inflammatory, pro-resolving, neuroprotective, and tissue-protective functions but are rapidly degraded by soluble epoxide hydrolase (sEH). EC5026 is a potent sEH inhibitor with no overt toxicity in several clinical trials. Here, we investigated whether impaired inflammation resolution contributes to GBM progression and systemic tissue wasting in mice bearing orthotopic CT2A glioblastoma tumors using EC5026. **Methods.** We utilized immunohistochemistry, and immunofluorescence of macrophage polarization markers, and fibrosis- and senescence-associated genes were assessed by qPCR and western blot analysis. **Results.** Immunohistochemistry revealed robust expression of the pro-resolving receptors LGR6, GPR37, and GPR18 throughout the GBM tumor microenvironment. Multiplex immunofluorescence demonstrated co-localization of LGR6 and GPR37 with Iba1-positive tumor-associated microglia and macrophages, while co-staining with iNOS and CD206 identified distinct pro-inflammatory and pro-resolving macrophage populations. Molecular profiling suggested reduced inflammatory signaling, decreased expression of fibrosis- and senescence-associated genes, and a shift toward a pro-resolving macrophage phenotype following EC5026 treatment. Histologically, EC5026 preserved skeletal muscle fiber cross-sectional area and reduced cachexia-associated markers in tumor-bearing mice. **Significance.** sEH inhibition reprograms the glioblastoma immune microenvironment toward a pro-resolving phenotype. **Conclusion.** Taken together, these findings suggest that failed resolution of inflammation contributes to both glioblastoma progression and GBM-induced muscle wasting. Furthermore, the localization of pro-resolving receptors to tumor-associated immune cells identifies previously unexplored resolution pathways in GBM and supports targeting the sEH/EET pathway as a strategy to enhance endogenous inflammation resolution, reprogram the tumor microenvironment, and mitigate glioblastoma-associated cachexia.