ABSTRACT

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RAGE Inhibitors as Alternatives to Dexamethasone for Managing Cerebral Edema Following Brain Tumor Surgery.

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Resection of brain tumors frequently causes injury to the surrounding brain tissue that exacerbates cerebral edema by activating an inflammatory cascade. Although corticosteroids are often utilized peri-operatively to alleviate the symptoms associated with brain edema, they increase operative morbidities and suppress the efficacy of immunotherapy. Thus, novel approaches to minimize cerebral edema caused by neurosurgical procedures will have significant utility in the management of patients with brain tumors. We have studied the role of the receptor for advanced glycation end products (RAGE) and its ligands on inflammatory responses to neurosurgical injury in mice and humans. Blood-brain barrier (BBB) integrity and neuroinflammation were characterized by Nanostring, flow cytometry, qPCR, and immunoblotting of WT and RAGE knockout mice brains subjected to surgical brain injury (SBI). Human tumor tissue and fluid collected from the resection cavity of patients undergoing craniotomy were also analyzed by single-cell RNA sequencing and ELISA. Genetic ablation of RAGE significantly abrogated neuroinflammation and BBB disruption in the murine SBI model. The inflammatory responses to SBI were associated with infiltration of S100A9-expressing myeloid-derived cells into the brain. Local release of pro-inflammatory S100A9 was confirmed in patients following tumor resection. RAGE and S100A9 inhibitors were as effective as dexamethasone in attenuating neuroinflammation. However, unlike dexamethasone and S100A9 inhibitor, RAGE inhibition did not diminish the efficacy of anti-PD-1 immunotherapy in glioma-bearing mice. These observations confirm the role of the RAGE axis in surgically induced neuroinflammation and provide an alternative therapeutic option to dexamethasone in managing post-operative cerebral edema.

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