Reactive astrocytes potentiate tumor aggressiveness in a murine glioma resection and recurrence model.


Abstract

BACKGROUND: Surgical resection is a universal component of glioma therapy. Little is known about the postoperative microenvironment due to limited preclinical models. Thus, we sought to develop a glioma resection and recurrence model in syngeneic immune-competent mice to understand how surgical resection influences tumor biology and the local microenvironment.

METHODS: We genetically engineered cells from a murine glioma mouse model to express fluorescent and bioluminescent reporters. Established allografts were resected using image-guided microsurgery. Postoperative tumor recurrence was monitored by serial imaging, and the peritumoral microenvironment was characterized by histopathology and immunohistochemistry. Coculture techniques were used to explore how astrocyte injury influences tumor aggressiveness in vitro. Transcriptome and secretome alterations in injured astrocytes was examined by RNA-seq and Luminex.

RESULTS: We found that image-guided resection achieved >90% reduction in tumor volume but failed to prevent both local and distant tumor recurrence. Immunostaining for glial fibrillary acidic protein and nestin showed that resection-induced injury led to temporal and spatial alterations in reactive astrocytes within the peritumoral microenvironment. In vitro, we found that astrocyte injury induced transcriptome and secretome alterations and promoted tumor proliferation, as well as migration.

CONCLUSIONS: This study demonstrates a unique syngeneic model of glioma resection and recurrence in immune-competent mice. Furthermore, this model provided insights into the pattern of postsurgical tumor recurrence and changes in the peritumoral microenvironment, as well as the impact of injured astrocytes on glioma growth and invasion. A better understanding of the postsurgical tumor microenvironment will allow development of targeted anticancer agents that improve surgery-mediated effects on tumor biology.

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