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The Reactive Astrocytes After Surgical Brain Injury Potentiates the Migration, Invasion, and Angiogenesis of C6 Glioma

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Background

Surgical resection is a key method for glioma treatment. This inherently invasive procedure alters the tumor microenvironment of glioma cells that cannot be removed by surgery. However, few studies have focused on the impact of this microenvironment change on the growth of glioma cells.

Methods

The authors preconstructed a surgical brain injury rat model, and then C6 glioma cells were transplanted. HE staining was used to observe the general morphology of tumor cells, and immunohistochemistry of MMP-2, MMP-9, GFAP, and CD31 was used to evaluate the invasiveness of glioma cells and activation of astrocytes after surgical brain injury. Subsequently, lysates, primary rat astrocytes were exposed to different temperature gradients. The supernatant was made into conditioned medium for culturing C6 glioma cells. The scratch test and transwell test were used to evaluate the migration and invasion of tumor cells.

Results

GFAP expression was stronger in surgical brain injury rats, C6 cells implanted in these rats showed stronger expression of MMP-2 and MMP-9, and CD31 was expressed in more microvessels. Astrocytes exposed to high temperatures of 40°C and 43°C expressed stronger GFAP, and C6 cells cultured in their supernatants had stronger scratch healing ability and the ability to cross transwell chambers.

Conclusions

The microenvironment changes caused by surgical brain injury will enhance the migration and invasion of glioma cells and increase the microvessel density in the tumor. This effect may be related to the activation of astrocytes caused by the thermal injury of bipolar coagulation during surgery.

Key words

C6 glioma cells; Reactive astrocytes; Surgical brain injury; Thermal injury

Abbreviations and Acronyms

BBB, Blood–brain barrier; GFAP, Glial fibrillary acidic protein; MMP-2, Matrix Metalloproteinase-2; MMP-9, Matrix Metalloproteinase-9; MVD, Mean optical density; MVD, Microvessel density; SBI, Surgical brain injury; SD, Sprague-Dawley

Previous article in this issue Next article in this issue

Introduction

Glioma is the most common intracranial malignant primary tumor and has an extremely dismal prognosis.1, 2, 3 The most extensive surgical resection is the key to improving the survival time of glioma patients. Multiple studies have supported the importance of gross total tumor resection, and patients with a greater degree of resection have a longer overall survival time.4 Over the last decade, with the development of neuroimaging, intraoperative imaging, and neuronavigation technology, neurosurgeons can be more invasive in the removal of gliomas. Gross total resection, even supratotal resection, has increasingly become the goal of surgery.5,6 However, even with radical treatment, most tumors usually recur at the margins after tumor resection in 90% of patients.7 This recurrence along the resection margin has a simple explanation that even in low-grade gliomas, the infiltrating glioma cells surrounding the primary tumor have already invaded the surrounding brain tissue several centimeters, no matter how extensive the surgical resection, those residual glioma cells in the surrounding brain tissue after surgery lead to recurrence.8,9

Surgery is inherently an invasive technique and inevitably causes injury to the surrounding brain tissue while removing tumors. This injury is called surgical brain injury (SBI), which is caused by neurosurgical maneuvers such as thermal damage caused by electrocauterization, incision, and brain retraction.10 SBI induces blood–brain barrier (BBB) disruption, astrogliosis, neuroinflammation, angiogenesis around the resection margin, and the release of growth factors and proteases.11, 12, 13 This means that residual glioma cell growth in a kind of microenvironment is altered by SBI and eventually forms recurrent tumors. However, little is known about the influence of the microenvironment changed by SBI on glioma cells.

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C6 Glioma Cells and Primary Rat Astrocyte Culture

C6 glioma cells were cultured in complete medium consisting of Dulbecco's modified Eagle's medium (DMEM Gibco) with 10% fetal bovine serum (FBS Sigma) and penicillin/streptomycin (100U/mL; Sigma) at 37°C and 5% CO_2.

Primary rat astrocytes were isolated from neonatal Sprague–Dawley (SD) rats following a previously described protocol.14 Briefly, rat brains were removed, and cortical hemisphere was cut into small pieces. The cortical sheet was transferred to phosphate buffered saline (PBS) ....

Results

All animals survived after the operation and were included in the statistics. ...

Discussion

There are 2 main findings in the present experiment as follows: 1) the microenvironment in surrounding brain tissue after SBI has effects on the growth of glioma, including accelerating the growth rate and promoting the migration of tumor cells. In addition, in the early stage after SBI, the microenvironment after SBI can increase the invasiveness of tumor cells and increase MVD in tumor tissue. 2) These effects may be due to the activation of astrocytes into reactive astrocytes by thermal ...

Conclusions

This experiment confirmed that the thermal injury of bipolar coagulation in surgical brain injury activates astrocytes in the surrounding brain tissue into reactive astrocytes to enhance glioma cell growth, migration, invasiveness, and angiogenesis in tumors at early time periods. ...

CRediT authorship contribution statement

Wenqiang Huang: Writing – review & editing, Writing – original draft. **Jinghui Li:** Writing – review & editing, Writing – original draft. **Xin Geng:** Data curation. **Shipeng Li:** Data curation. **Yonghong Zou:** Resources. **Yao Li:** Visualization. **Gang Jing:** Visualization. **Hualin Yu:** Conceptualization, Methodology. ...

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Wenqiang Huang and Jinghui Li contributed equally to this work.

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