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# Disease Mechanisms in Neuroscience

## Glutamate and the growth of brain tumors

Malignant gliomas are among the deadliest of cancers: even when treated aggressively, patients with these brain tumors have a median survival of less than 12 months. Being confined, together with normal brain tissue within the cranial cavity, malignant gliomas grow at the expense of precious brain tissue, which is destroyed as they invade. How does this occur? Two years ago, Sontheimer and his colleagues (Ye and others 1999; Ye and Sontheimer 1999) showed that glioma cells, including human glioma cells, release the excitatory neurotransmitter glutamate, in part due to compromised glutamate transport, with the result that glutamate in the cells' vicinity can reach levels that can be injurious to neurons. These observations suggested that a previously unrecognized mechanism—excitotoxicity—might play a role in the growth of brain tumors and the destruction of normal brain tissue that accompanies it. Now another article, by Nedergaard and her coworkers (Takano and others 2001), presents additional evidence indicating that glutamate release can promote the growth of malignant gliomas. In this recent study, Takano and others studied C6 glioma cell lines differing in their potential to secrete glutamate, and subcloned cell lines that either actively released glutamate (C6Glu<sup>+</sup>) cells or showed enhanced uptake of glutamate (C6Glu<sup>-</sup> cells). Conditioned medium obtained from C6Glu<sup>+</sup> cells triggered rapid increases in intracellular calcium within cultured neurons, whereas conditioned medium obtained from C6Glu<sup>-</sup> cells evoked much smaller changes. The addition of C6Glu<sup>+</sup> cell aggregates resulted in a highly significant loss of neurons within cortical cultures. The effect of glioma glutamate release in the brain was evaluated

following implantation of cell clones within the striatum of adult rats; these experiments demonstrated that glutamate-secreting gliomas expanded faster and became larger, suggesting that they have a growth advantage. Moreover, administration of the NMDA antagonist MK801, as well as the uncompetitive NMDA receptor antagonist memantine, tended to slow tumor expansion.

Taken together, these three studies provide strong evidence for a role of glutamate in promoting the growth of malignant gliomas. As pointed out in these three articles and by Rothstein and Brem (2001), discovery of this novel mechanism points to a number of possible approaches to therapy, including glutamate receptor blockade, stimulation of neuronal or glial glutamate uptake, inhibition of glutamate synthesis, or inhibition of glutamine synthetase. We will undoubtedly be hearing more about glutamate excitotoxicity and brain tumors and about these therapeutic strategies in the near future.

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