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### Glutamate and the biology of gliomas.

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#### Abstract

Several important and previously unrecognized roles for the neurotransmitter glutamate in the biology of primary brain tumors have recently been elucidated. Glutamate is produced and released from glioma cells via the system x(c) (-) cystine glutamate transporter as a byproduct of glutathione synthesis. Glutamate appears to play a central role in the malignant phenotype of glioma via multiple mechanisms. By binding to peritumoral neuronal glutamate receptors, glutamate is responsible for seizure induction and similarly causes excitotoxicity, which aids the expansion of tumor cells into the space vacated by destroyed tissue. Glutamate also activates ionotropic and metabotropic glutamate receptors on glioma cells in a paracrine and autocrine manner.  $\alpha$ -Amino-3-hydroxy-5-methyl-4-isoaxazolepropionate acid (AMPA) glutamate receptors lack the GluR2 subunit rendering them Ca(2+) permeable and capable of activating the AKT and MAPK pathways. Furthermore, these receptors are critical in aiding the invasion of glioma cells into normal brain. AMPA-Rs accumulate at focal adhesion sites where they may indirectly mediate interactions between the extracellular matrix and integrins. Glutamate receptor stimulation results in activation of focal adhesion kinase, which is critical to the regulation of growth factor and integrin-stimulated cell motility and invasion. The multitude of effects of glutamate on glioma biology supports the rationale for pharmacological targeting of glutamate receptors and transporters. Several ongoing and recently completed clinical trials are exploring the therapeutic potential of interrupting glutamate-mediated brain tumor growth. © 2010 Wiley-Liss, Inc.

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