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Signal transduction for proliferation of glioma cells in vitro occurs predominantly through a protein kinase C-mediated pathway.

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Abstract
Previous work has demonstrated that glioma cells have very high protein kinase C (PKC) enzyme activity when compared to non-malignant glia, and that their PKC activity correlates with their proliferation rate. The purpose of this study was to determine whether the elevated PKC activity in glioma is secondary to an autonomously active PKC isoform implying oncogenic transformation, or whether this activity is driven by upstream ligand-receptor tyrosine kinase interactions. We treated established human glioma cell lines A172, U563 or U251 with either the highly selective PKC inhibitor CGP 41 251, or with genistein, a tyrosine kinase inhibitor. The proliferation rate and PKC activity of all the glioma lines was reduced by CGP 41 251; the IC50 values for inhibiting cell proliferation corresponded to the IC50v values for inhibition of PKC activity. Genistein also inhibited cell proliferation, with IC50 proliferation values approximating those for inhibition of tyrosine kinase activity in cell free protein extracts. Importantly, in genistein-treated cells, downstream PKC enzyme activity was dose dependently reduced such that the correlation coefficient for effects of genistein on proliferation rate and PKC activity was 0.92. These findings suggest that upstream tyrosine kinase linked events, rather than an autonomously functioning PKC, result in the high PKC activity observed in glioma. Finally, fetal calf serum (FCS) evoked a strong mitogenic effect on glioma cell lines. This mitogenic activity was completely blocked by CGP 41 251, suggesting that although the many mitogens in FCS for glioma cells signal initially through genistein-inhibitable tyrosine kinases, they ultimately channel through a PKC-dependent pathway. We conclude that proliferative signal transduction in glioma cells occurs through a predominantly PKC-dependent pathway and that selectively targeting this enzyme provides an approach to glioma therapy.

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