Inhibition of epidermal growth factor receptor-associated tyrosine kinase blocks glioblastoma invasion of the brain.

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Abstract

OBJECTIVE: Glioblastoma multiforme is a malignant primary brain tumor associated with short patient survival despite aggressive treatment, in part because of its propensity to aggressively infiltrate into brain tissue. Glioblastoma multiforme is also unique because it is the only non-epithelial human tumor for which excessive activation of epidermal growth factor receptor (EGFR) has been consistently linked to tumor growth and patient survival, and EGFR activation promotes glioblastoma multiforme infiltration in vitro.

METHODS: Cocultures of human glioblastoma spheroids (derived from three separate patients) and fetal rat brain aggregates were examined for infiltration using confocal microscopy, in the presence of 0 to 100 μmol/L genistein, a tyrosine kinase (TK) inhibitor, and 3 μmol/L tyrphostin A25, a specific EGFR-TK inhibitor.

RESULTS: Infiltration (not attachment) was completely inhibited by genistein at 10 μmol/L, the IC20 for monolayer growth inhibition in two cell lines. Tyrphostin A25 at 3 μmol/L (the IC20 for monolayers) reduced invasion in a third cell line from 38.8 +/- 6.1% invasion-hour per hour (n = 5) to 2.9 +/- 1.2% invasion-hour per hour (n = 6) (P = 0.0002, two-tailed t test, 93% inhibition), and from 0.54 +/- 0.065% per hour (slope) to 0.028 +/- 0.018% per hour (P = 0.00001, 95% inhibition). Maximal percent invasion was reduced from 100 +/- 0 to 7.4 +/- 5.6% of the fetal rat brain aggregate. No change was detected in EGFR-associated tyrosine phosphorylation at those doses in monolayers by 32P immunolabeling, consistent with the known effects of low concentrations of TK inhibitors. An increase in expression of wild-type and truncated EGFR was demonstrated by Western blotting. Invasion was equally well inhibited by a monoclonal antibody to the high-affinity ligand binding domain of EGFR and not by antibody to an inactive domain.

CONCLUSION: Our observations support the role of EGFR activation as a determinant by which glioblastoma invades normal brain tissue, and we show that invasion can be effectively inhibited at much lower concentrations of TK inhibitors than are necessary for growth suppression.

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