Bimodal anti-glioma mechanisms of cilengitide demonstrated by novel invasive glioma models.


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Abstract
Integrins are expressed in tumor cells and tumor endothelial cells, and likely play important roles in glioma angiogenesis and invasion. We investigated the anti-glioma mechanisms of cilengitide (EMD121974), an \( \alpha v \beta 3 \) integrin inhibitor, utilizing the novel invasive glioma models, J3T-1 and J3T-2. Immunohistochemical staining of cells in culture and brain tumors in rats revealed positive \( \alpha v \beta 3 \) integrin expression in J3T-2 cells and tumor endothelial cells, but not in J3T-1 cells. Established J3T-1 and J3T-2 orthotopic gliomas in athymic rats were treated with cilengitide or solvent. J3T-1 gliomas showed perivascular tumor cluster formation and angiogenesis, while J3T-2 gliomas showed diffuse single-cell infiltration without obvious angiogenesis. Cilengitide treatment resulted in a significantly decreased diameter of the J3T-1 tumor vessel clusters and its core vessels when compared with controls, while an anti-invasive effect was shown in the J3T-2 glioma with a significant reduction of diffuse cell infiltration around the tumor center. The survival of cilengitide-treated mice harboring J3T-1 tumors was significantly longer than that of control animals (median survival: 57.5 days and 31.8 days, respectively, \( P < 0.005 \)), while cilengitide had no effect on the survival of mice with J3T-2 tumors (median survival: 48.9 days and 48.5, \( P = 0.69 \)). Our results indicate that cilengitide exerts a phenotypic anti-tumor effect by inhibiting angiogenesis and glioma cell invasion. These two mechanisms are clearly shown by the experimental treatment of two different animal invasive glioma models.


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