Effects of Anti-Angiogenesis on Glioblastoma Growth and Migration: Model to Clinical Predictions

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Glioblastoma multiforme (GBM) causes significant neurological morbidity and short survival times. Brain invasion by GBM is associated with poor prognosis. Recent clinical trials of bevacizumab in newly-diagnosed GBM found no beneficial effects on overall survival times; however, the baseline health-related quality of life and performance status were maintained longer in the bevacizumab group and the glucocorticoid requirement was lower. Here, we construct a clinical-scale model of GBM whose predictions uncover a new pattern of recurrence in 11/70 bevacizumab-treated patients. The findings support an exception to the Folkman hypothesis: GBM grows in the absence of angiogenesis by a cycle of proliferation and brain invasion that expands necrosis. Furthermore, necrosis is positively correlated with brain invasion in 26 newly-diagnosed GBM. The unintuitive results explain the unusual clinical effects of bevacizumab and suggest new hypotheses on the dynamic clinical effects of migration by active transport, a mechanism of hypoxia-driven brain invasion.


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In malignant brain tumors invasive glioma cells become associated with several brain compartments: blood vessels, white matter fibers, brain parenchyma, and meninges. How individual microanatomical patterns of invasion lead to eventually deadly tumor growth, and influence disease progression and clinical outcomes remain poorly understood. We have investigated how early perivascular growth of brain tumor cells affects larger patterns of glioma growth and the formation of macroscopic tumors. As glioma cells migrate on brain vessels within the highly vascularized brain, we conclude that in these cases the formation of macroscopic tumors can be explained by the exclusive growth of glioma cells on brain vessels; thus, we also studied tumor growth in response to anti-angiogenic therapy. Orthotopically implanted rodent and human glioma stem cells invaded the brain and proliferated within the potential brain perivascular space. This form of brain tumor growth and invasion also characterized endogenous mouse brain tumors, primary human glioblastoma, and peripheral cancer metastasis to the human brain. Perivascularly invading brain tumors become vascularized by pre-existing microvessels as individual gliomas cells use the potential perivascular space as a pathway for tumor invasion. Agent-based computational modeling recapitulated biological perivascular glioma growth without the need to specifically account for parameters modeling neoangiogenesis. As predicted by the computational model, the requirement for neoangiogenesis in our various glioma models was tested by treating animals with angiogenesis inhibitors bevacizumab and DC101. These inhibitors induced the expected vessel normalization, but failed to reduce tumor growth or improve survival of mice bearing orthotopic or endogenous gliomas; this treatment was also shown to preserve the structure of brain vessels and exacerbate brain tumor invasion. We are also examining the progression of cell division in relation to the different compartments occupied by tumor cells to test the “growth or grow” hypothesis of tumor growth. Our results provide compelling experimental evidence supporting a mechanism of macroscopic glioma formation that relies on the it-


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Motility Determines Growth, Recurrence, and Treatment Response: Insights From a Mathematical Model of GBM

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