MS15: Multiscale Modeling in Cancer: From Genotype to Phenotype II

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.

Mechanisms of Glioma Formation: Exploring Glioma Growth Through Dialectic Biological-Computational Approaches

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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-

erative invasion of blood vessels and consequent filling in of brain matter situated between any two blood vessels. In addition, our data also indicate a potential pathway to explain the recently described failure of clinically used antiangiogenics to extend the survival of human glioma patients.

Modeling of the Resistance to Treatments for Gastro-Intestinal Stromal Tumors

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Gastro-intestinal stromal tumor can create lesions to the liver in the metastatic phase. The evolution of the disease is usually followed using CT-scans and targetted therapies (anti-angiogenic drugs and tyrosin kinase inhibitors) are used to control the growth. These treatment have most of the time a good efficiency but unfortunately at sometime a relapse occurs. Based on an accurate analysis of medical images, we provide a patient-dependent model that reproduces qualitatively and quantitatively the spatial tumor evolution, as followed up by the clinical data. In particular, specific aspects of tumor growth as spatial heterogeneity and treatment failures can be explained by our model. We will present the construction of the model as well as some well-posedness results.

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

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Glioblastoma multiforme (GBM) is a malignant brain tumor with poor prognosis and inherent propensity to invade the brain. We apply a concise system of partial differential equations that models GBM biology at the scale of magnetic resonance imaging, to replicate the patterns of recurrence of GBM treated by anti-angiogenesis. The findings reveal that tumor motility determines tumor growth and recurrence and uncover a novel principle linking the mechanisms of brain invasion to tumor biology.