Russell Rockne
University of Washington Department of Pathology, Department of Applied Mathematics
e-mail: rockne@uw.edu
Susan Massey
University of Washington Department of Applied Mathematics
Maciej M. Mrugala
University of Washington Department of Neurology
Alexandar R. A. Anderson
Moffitt Cancer Center Integrative Mathematical Oncology
Kristin R. Swanson
University of Washington Department of Pathology, Department of Applied Mathematics

Response to anti-angiogenic therapy in human brain tumors: the role of the microenvironment and heterogeneity

Background: Gliomas are diffuse and invasive primary brain tumors that are notoriously difficult to treat and uniformly fatal. Angiogenesis is the process of neovascularization and is a hall mark of glioblastoma, which are considered amongst the most angiogenic of tumors. This suggests that interactions between glioma cells and the cascade of biological events leading to tumor-induced neoangiogenesis play an important role in aggressive tumor formation and progression.

Anti-angiogenic therapies have been used in the treatment of gliomas with spurious results ranging from no apparent response to significant imaging improvement with extremely diffuse patterns of tumor recurrence. The clinical task of assessing a patients response to brain tumor therapy is difficult, and the topic of much current debate. Paradoxically, anti-angiogenic therapies likely increase the efficiency of tumor vasculature through normalization, leading to a resolution of abnormality on imaging, while at the same time increasing the tumors invasive phenotype and actually promote rather than hinder tumor growth. As a result, response to anti-angiogenic therapies is inadequately assessed by current imaging techniques but may be interpretable by multi-modality approaches combined with mathematical modeling.

Methods: Much of the difficulty in improving the outcomes of patients with gliomas lies with the extensive invasive potential and incredible phenotypic heterogeneity of these tumors. To quantitatively explore these tumor-microenvironment interactions, we extend our previous experience with biologically-based mathematical models for glioma growth and invasion to explicitly incorporate the interactions of normoxic glioma cells, hypoxic glioma cells, vascular endothelial cells, diffusible angiogenic factors and the formation of necrosis, hallmarks of the histological diagnosis of glioma and investigate the role and effects of anti-angiogenic therapies in silico.

Results: Using in silico experimentation, we find that anti-angiogenic therapies drastically decrease the hypoxic phenotype and promote the invasive phenotype. However, the degree and characterization of response to anti-angiogenic therapies depends on the relative extent of invasion and proliferation of the tumor, and can vary from one patient to the next. Moreover, these effects vary across histologic

grades and may promote malignant progression from low to higher grades. These results suggest that a combination of therapies must be used if anti-angiogenic therapies are to be effective in human gliomas.