Mechanisms of glioma formation: iterative perivascular glioma growth and invasion leads to tumor progression, VEGF-independent vascularization, and resistance to antiangiogenic therapy.


Abstract

As glioma cells infiltrate the brain they become associated with various microanatomic brain structures such as blood vessels, white matter tracts, and brain parenchyma. How these distinct invasion patterns coordinate tumor growth and influence clinical outcomes remain poorly understood. We have investigated how perivascular growth affects glioma growth patterning and response to antiangiogenic therapy within the highly vascularized brain. Orthotopically implanted rodent and human glioma cells are shown to commonly invade and proliferate within brain perivascular space. This form of brain tumor growth and invasion is also shown to characterize de novo generated endogenous mouse brain tumors, biopsies of primary human glioblastoma (GBM), and peripheral cancer metastasis to the human brain. Perivascularly invading brain tumors become vascularized by normal brain microvessels as individual glioma cells use perivascular space as a conduit for tumor invasion. Agent-based computational modeling recapitulated biological perivascular glioma growth without the need for neoangiogenesis. We tested the requirement for neoangiogenesis in perivascular glioma by treating animals with angiogenesis inhibitors bevacizumab and DC101. These inhibitors induced the expected vessel normalization, yet failed to reduce tumor growth or improve survival of mice bearing orthotopic or endogenous gliomas while exacerbating brain tumor invasion. Our results provide compelling experimental evidence in support of the recently described failure of clinically used antiangiogenics to extend the overall survival of human GBM patients.

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