Microarray analysis verifies two distinct phenotypes of glioblastomas resistant to anti-angiogenic therapy.

Department of Neurosurgery, University of California at San Francisco.

Abstract

**PURPOSE:** To identify mechanisms and mediators of resistance to anti-angiogenic therapy in human glioblastoma.

**EXPERIMENTAL DESIGN:** We performed microarray gene expression analysis and immunohistochemistry comparing 21 recurrent glioblastomas progressing during anti-angiogenic treatment with VEGF neutralizing antibody bevacizumab to paired pre-treatment tumors from the same patients.

**RESULTS:** Microarray analysis revealed that bevacizumab-resistant glioblastomas (BRGs) had 2 clustering patterns defining subtypes that reflect radiographic growth patterns. Enhancing BRGs (EBRGs) exhibited MRI enhancement, a long-established criterion for glioblastoma progression, and expressed mitogen-activated protein kinases, neural cell adhesion molecule-1 (NCAM-1), and aquaporin 4. Compared to their paired pre-treatment tumors, EBRGs had unchanged vascularity and hypoxia, with increased proliferation. Non-enhancing BRGs (NBRGs) exhibited minimal MRI enhancement but had FLAIR-bright expansion, a newer criterion for glioblastoma recurrence since the advent of anti-angiogenic therapy, and expressed integrin alpha5, laminin, fibronectin1, and PDGFRbeta. NBRGs had less vascularity, more hypoxia, and unchanged proliferation than their paired pre-treatment tumors. Primary NBRG cells exhibited more stellate morphology with a 3-fold increased shape factor and were nearly 4-fold more invasive in matrigel chambers than primary cells form EBRGs or bevacizumab-naive glioblastomas (P less than 0.05).

**CONCLUSION:** Using microarray analysis, we found two resistance patterns during anti-angiogenic therapy with distinct molecular profiles and radiographic growth patterns. These studies provide valuable biologic insight into the resistance that has limited anti-angiogenic therapy to date.

PMID: 22472177 [PubMed - as supplied by publisher]