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Mediators of glioblastoma resistance and invasion during antivascular endothelial growth factor therapy.

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Abstract

PURPOSE: Vascular endothelial growth factor (VEGF) has been identified as a critical regulator of angiogenesis. Currently, several different strategies are being used to target the VEGF-VEGF receptor signal transduction pathway in glioblastoma. Although anti-VEGF therapy seems be effective in normalizing abnormal tumor vasculature, leading to an enhanced response to radiation and chemotherapy, tumors eventually become resistant to the therapy and adopt a highly infiltrative and invasive phenotype.

EXPERIMENTAL DESIGN: In the present study, we evaluated the effects of anti-VEGF therapy (bevacizumab) on glioblastoma invasion both in vitro and in vivo and evaluated the angiogenesis- and invasion-related mediators of developed resistance to this therapy.

RESULTS: We found that glioblastoma tumors escaped from antiangiogenic treatment by (a) reactivating angiogenesis through up-regulation of other proangiogenic factors and (b) invading normal brain areas, which was seen in association with up-regulation of matrix metalloproteinase (MMP)-2, MMP-9, and MMP-12; secreted protein, acidic, cysteine-rich; and tissue inhibitor of metalloproteinase 1. In addition to the paracrine effects of VEGF on endothelial cells, autocrine VEGF signaling seemed to regulate glioblastoma invasion because anti-VEGF therapy increased tumor invasiveness in vitro.

CONCLUSIONS: Collectively, these findings reinforce the importance of VEGF in regulating tumor invasion and identify potential mediators of resistance to targeted VEGF therapy. These results will be important for developing novel combination therapies to overcome this resistance phenotype.

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