Title: Tumors that respond poorly to bevacizumab therapy show upregulation of angiogenesis genes in glioblastoma.

Despite surgical-resection and radio-chemotherapy glioblastoma (GBM), the most common primary brain tumor in adults, has a median survival of 15-month median survival and a recurrence rate of 90% following primary treatment. The common treatment for recurrent-GBM includes bevacizumab, a monoclonal antibody toward vascular endothelial growth factor-A, as it reduces brain edema and improves the quality of life but only improves survival in only a small percentage of patients. To find predictors of poor response to bevacizumab, we performed RNA-sequencing on multiple GBM patient-derived xenograft (PDX) tumors after orthotopic propagation in athymic nude mice. The study was repeated, and once PDX-tumors were established, mice were treated with bevacizumab or vehicle until euthanasia. PDX-tumors were grouped based on their survival. Bioinformatic analysis of RNA-sequencing data from tumors in untreated mice demonstrated differential gene expression poor responders (decreased survival) relative to good-responders along with upregulation of an angiogenesis gene set. Within this gene set, multiple genes known to be regulated by the early growth response 1 (*EGR1*) transcription factor were identified; two were selected for further study based on their role in promoting cancer cell migration and proliferation, *RAMP3* (accessory-receptor for adrenomedullin) and *CHRNA7* (cholinergic-receptor-nicotinic-α7-subunit, or α7-nAChR). Immunostaining/multiplex staining validated the increased expression of EGR1 in tumor cells from poor-responder tumors. Data mining further revealed shorter patient survival in GBM patients with upregulated *EGR1* or *CHRNA7* mRNA. In summary, PDX-tumors with upregulated expression of an angiogenesis gene set demonstrated a poor response to bevacizumab; therefore, these genes may be used to predict bevacizumab response.