

Commentary

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Commentary: Periostin (POSTN) Regulates Tumor Resistance to Antiangiogenic Therapy in Glioma Models

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ABSTRACT

Glioblastoma (GBM) are highly vascularized, invasive brain tumors with a dismal prognosis. Despite surgical de-bulking of the tumor mass followed by concomitant intensive chemo/radiotherapy, GBM patients exhibit poor survival rates (REF). The hallmark presence of microvascular proliferation in GBM has attracted vast interest in the use of antiangiogenic therapies. Bevacizumab a humanized recombinant monoclonal antibody against VEGF-A was approved by the FDA for the treatment of recurrent GBM. However, several recent studies have reported the lack of a survival benefit suggesting tumors have both intrinsic and acquired resistance to anti-VEGF therapy^{1,2}. Studies suggest mesenchymal transition and hypoxia signaling as two major pathways associated with the development of resistance to anti-VEGF therapy. Recently, we reported that the glioma treated with bevacizumab have higher periostin (POSTN) expression than control tumors in a murine glioma tumor models³. In this commentary, we review our recent findings as well as the role of POSTN in antiangiogenic therapy resistance in glioma.

A previous study from our group found that anti-VEGF-A therapy increases invasive properties both in a GBM stem cell line (GSC11) and in glioma U87 xenograft tumors⁴. By using microarray analysis we found several genes including POSTN that were upregulated in bevacizumab resistant tumors. In this current study, we investigated the relationship between POSTN expression and bevacizumab resistance in mouse glioma stem cells xenograft tumors. In our model of anti-VEGF-A resistance³, GSC11 and U87 tumors treated with bevacizumab expressed higher POSTN levels than control tumors. Periostin (POSTN; osteoblast-specific factor 2) is a 90-kDa ECM protein containing an amino-terminal EMI domain, tandem repeats of four fasciclin domains, and a carboxy-terminal (C-terminal) domain, including a heparin binding site⁵. It has been reported that during epithelial-to mesenchymal transition (EMT), POSTN regulates several EMT markers including vimentin, fibronectin, and matrix metalloproteinase (MMP)-9⁶. In addition to EMT markers, POSTN induces angiogenesis in endothelial cells⁷, and in gastric cancer cells under hypoxia conditions⁸. In GBM, POSTN is highly expressed when compared to normal brain⁹ and is associated with glioma recurrence and/or tumor progression¹⁰. Bevacizumab-resistant recurrent tumors were very large and had decreased oxygen supply in the core of the tumor as indicated by expression of the hypoxia marker HIF-1 alpha. In our study, we evaluated the potential consequence of bevacizumab on the promotion of tumor hypoxia and an aggressive glioblastoma phenotype.

We used PCR based arrays and identified POSTN regulated mesenchymal and angiogenesis signaling in glioma stem cells (GSCs).

In our results, depletion of POSTN decreased invasion and secretion of VEGF in GSCs. Treatment of POSTN in GSCs increased invasion. Furthermore, expression of EMT-related genes such as N-cadherin, caveolin-1 and HIF-1 alpha which were decreased after POSTN knockdown. In POSTN depleted tumors, treatment with bevacizumab, increased median survival and decreased tumor size compared to treatment with bevacizumab treatment of POSTN expressing tumors. In addition to the main source of tumor vascularization, hypoxia has an established role in the self-renewal and expansion of the GSC pool. Depletion of POSTN reduces the HIF-1 alpha expression in mouse xenograft tumors. In summary the expression of HIF-1 alpha, a key marker of resistance to anti-VEGF-A therapy, was lower in the POSTN shRNA groups than control in the xenograft glioma models.

In addition to the mechanisms mentioned above, we cannot exclude the fact that tumor microenvironmental factors also can promote GSC transdifferentiation into endothelial-like cells for the formation of new blood vessels. Importantly, GSCs can cause recruitment of immune cells, in particular, tumor-associated macrophages (TAMs) to promote angiogenesis¹¹. We and other have shown that bevacizumab treatment increased immune cell infiltration into glioma tumors. To determine the POSTN expression in the xenografts, we used double immunofluorescence staining for the stem cell marker nestin or the macrophage marker F4/80 along with POSTN. We observed that POSTN was co-stained with nestin (tumor stem cells) but not with F4/80 (macrophage). This staining results suggest that the POSTN expression is predominant in cancer cells rather than the infiltrating macrophages. In our study, bevacizumab treatment increased TGFβ1 expression in murine GSC272 and GSC11 xenografts. However, in future studies we would need to take in account of the POSTN and their role on induction of angiogenesis via recruitment of endothelial cells and functional assays such as angiogenesis tube formation assays which will clarify the direct and indirect role of POSTN in induction of angiogenesis in glioblastoma. POSTN interacts with several integrin receptors such as αvβ1 and αvβ3¹², and it has been reported that POSTN recruits alternatively activated TAMs into the stem cell niche. Integrin αvβ3 expression on monocytes and macrophages is the main receptor for POSTN-mediated TAM recruitment¹³. Inhibition of integrin αvβ3 and integrin αvβ5 prevented bevacizumab-induced invasion in orthotopic glioma models which express these integrins at high levels¹⁴. Interestingly, in our study, we found that differential expression of integrin β1 and integrin β3 in GSCs which play a role in cancer stem cell invasion. In particular, anti-integrin β1 antibody inhibits invasion induced by the treatment of recombinant TGFβ1 and POSTN, whereas integrin β3 blockade had no effect on TGFβ1 and POSTN induced invasion. Treatment of GSCs

with TGFβ1 induces POSTN secretion and phosphorylation of SMAD3 and SMAD2. Furthermore, TGFβ1 increased the expression of HIF-1 alpha, VEGF-A, and STAT3 such as crucial factors involved in angiogenesis, hypoxia, and stem cell self-renewal and invasion via POSTN. However, in future studies, it will be interesting to study the combined role of POSTN and TGFβ1 in GSCs invasion and migration. The role of TGFβ in EMT, cell survival, angiogenesis, and invasion has been well established in several solid tumors^{15,16}. Previous studies in other organs have shown TGFβ1 induced POSTN and BMP2 during bone formation and adipocyte differentiation^{17,18}. Both BMP2 and POSTN have been detected in glioma cell cultures, cerebrospinal fluid and brain tumor biopsy samples from glioma patients¹⁹. Recent studies have confirmed tumor stromal POSTN expression in breast cancers, melanoma^{20,21}. In breast cancer, a small subset of metastatic cancer stem cells induce POSTN expression in the stroma of lungs for successful metastasis and colonization of lungs²¹. Collectively, these studies establish the role of POSTN in tumor stem cell maintenance and invasion. In GBM, tumor-associated macrophages (TAM) density positively correlates with POSTN protein levels and disrupting POSTN markedly reduced TAM density and improved survival and decreased tumor growth in a mouse GSCs xenograft model¹³. TGFβ1 promoted mesenchymal gene expression, especially in bevacizumab-resistant GSC cells²². In our study, we found a bidirectional signaling of TGFβ1 and POSTN in glioma stem cells and their regulation of GSCs invasion, induction of angiogenesis especially in bevacizumab-resistant GSC cells. In conclusion, in addition to TGFβ targeting, POSTN is an attractive alternative target for anti-VEGF resistant tumors, to inhibit glioma invasion, and interrupt communication between cancer stem cells and the tumor microenvironment to prevent glioma growth and progression.

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