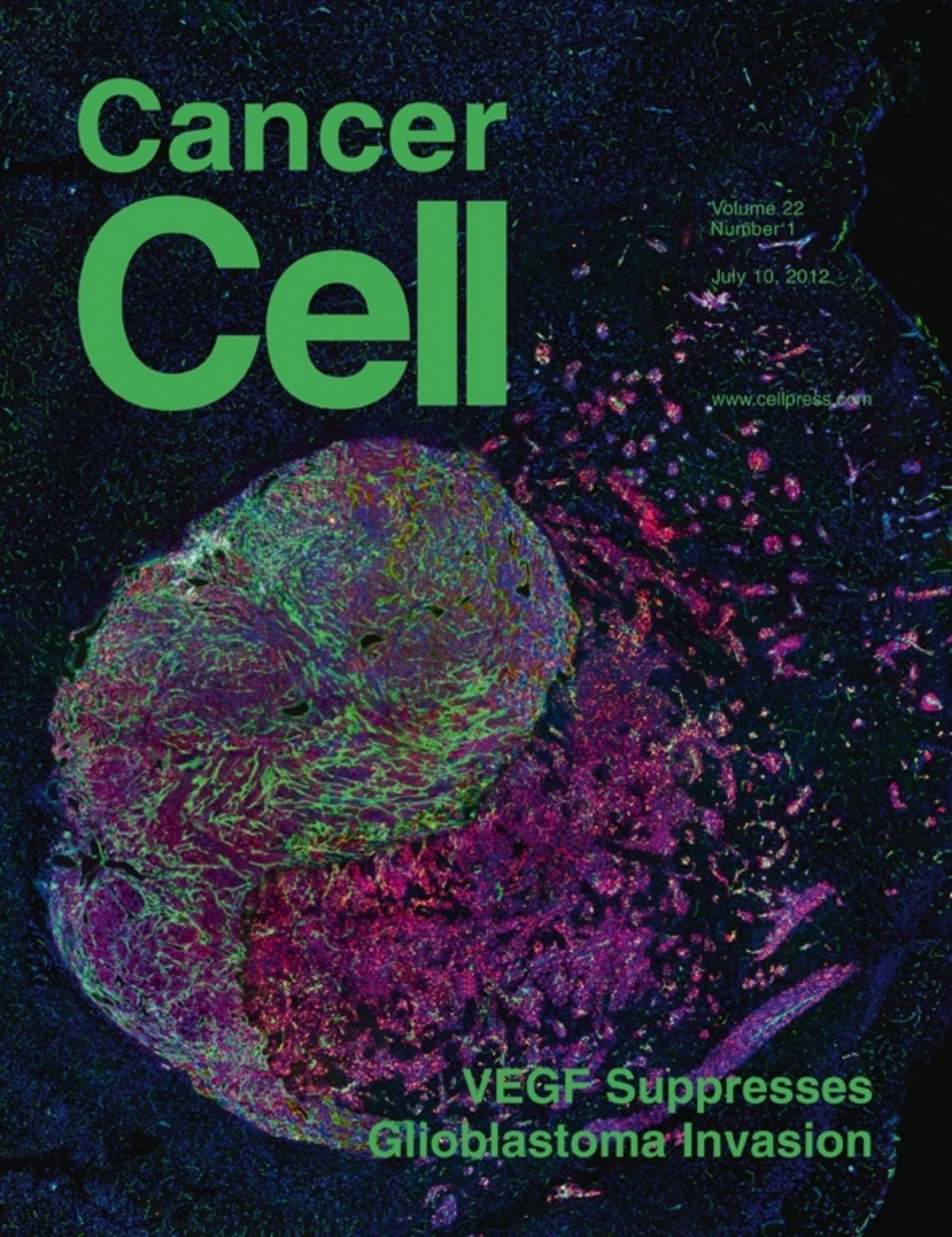
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VEGF Suppresses
Glioblastoma Invasion

Receptor Talk and Tumor Cell Walk in Glioblastoma

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In this issue of *Cancer Cell*, Lu et al. describe unconventional molecular interactions in glioblastoma cells that provide a mechanism for how anti-vascular endothelial growth factor therapy may promote mesenchymal transition of glioblastoma cells and increase tumor invasion.

Suppression of tumor angiogenesis using neutralizing antibodies against vascular endothelial growth factor (VEGF) initially appeared to be a straightforward strategy to starve the tumor and stop metastatic spread. Indeed, the anti-VEGF neutralizing antibody bevacizumab has been approved for the treatment of metastatic colorectal cancer, non-squamous non-small cell lung cancer, glioblastoma multiforme, and metastatic renal carcinoma. Disappointingly, a significant fraction of bevacizumab-treated patients carry tumors that are insensitive to this therapy or acquire resistance relatively quickly (Bergers and Hanahan, 2008). The worrisome findings that antiangiogenic therapy may increase tumor invasiveness and metastatic spread, described by the Kerbel and Casanova groups (Ebos et al., 2009; Pàez-Ribes et al., 2009), have further complicated the application of anti-VEGF treatment.

Data from the Bergers laboratory (Lu et al., 2012), in this issue of *Cancer Cell*, provide a possible explanation for the increased invasiveness seen with anti-VEGF therapy. Accordingly, blocking VEGF leads to increased activity of the hepatocyte growth factor (HGF) receptor MET, and elimination of both MET and VEGF expression from glioblastoma leads to increased survival in experimental models (Lu et al., 2012).

VEGF was originally described by Harvard Medical School researchers Donald Senger and Harold Dvorak as vascular permeability factor (VPF) and subsequently identified as an endothelial growth factor by Napoleone Ferrara (Dvorak, 2006). Overwhelming evidence in animal models and patients shows that bevacizumab suppresses pathological tumor vascularization. VEGF binds to two receptor tyrosine kinases, of which VEGF receptor 2 (VEGFR2) is primarily responsible for VEGF's effects on endothelial cells in blood vessels (Koch et al., 2011). Although initially perceived as endothelial cell-specific, refined reagents and analyses clearly show that VEGFR2 is expressed also in nonendothelial cells. Indeed, Lu et al. (2012) show that VEGFR2 is expressed in glioblastoma cells. VEGF-targeted therapy therefore may lead to adverse and unexpected effects by suppressing VEGFR2 on nonendothelial cells.

Glioblastoma multiforme is the most aggressive form of brain cancer, with a median survival of 18 months (Chamberlain, 2011). Treatment of recurrent glioblastoma with bevacizumab prolongs progression-free survival, particularly in older patients. The effect of bevacizumab is exerted atleast in part by reducing brain edema, demonstrating that neutralization of VEGF/VPF efficiently seals leaky tumor vessels. That the reduced permeability impairs contrast-enhanced magnetic resonance imaging, resulting in a false impression of reduced tumor dimensions, has confounded conclusions regarding the clinical benefit of bevacizumab therapy. In agreement with data from animal models (Ebos et al., 2009; Pàez-Ribes et al., 2009), there are indications for increased invasiveness of the cancer in bevacizumab-resistant glioblastoma, resulting in therapy-inaccessible, infiltrative growth along blood vessels (Chamberlain, 2011).

Interestingly, Lu et al. (2012) find that VEGFR2 is engaged in a constitutive complex with MET, which also includes a cytoplasmic phosphotyrosine phosphatase, PTP1B. PTPs, including PTP1B, serve dual roles in cancer and are implicated as both tumor suppressors and promoters of oncogenesis (Julien et al., 2011). In the scenario described by Lu et al. (2012), VEGFR2 directs the action of PTP1B toward HGF-activated MET, leading to MET dephosphorylation and thereby suppression of cell motility. Blocking VEGF through bevacizumab treatment unleashes HGF/MET activity by disengaging the phosphatase from the VEGFR2/MET complex. The fullblown MET activity in its turn promotes invasiveness (Figure 1), involving induction of a gene transcription program in the tumor, reminiscent of epithelial-to mesenchymal transition. Importantly, the Lu et al. (2012) study shows increased MET phosphorylation and, therefore, activity in gliomas from bevacizumab-treated patients.

The study by Lu et al. (2012) raises several critical questions regarding growth factor signaling. For example, does VEGFR2 signaling have cell-specific traits? VEGFR2 stimulates a wide spectrum of signaling pathways in endothelial cells resulting in survival, proliferation, migration, and formation of lumenized 3D vessel structures (Koch et al., 2011). This biology involves several of the most well-known signaling pathways, such as the RAS-RAF-ERK pathway and the PI3K/AKT pathway, which operate downstream of most growth factor receptors in most cell types. Surprisingly, VEGFR2 does not seem to contribute as a positive regulator in glioma cells. And why does VEGFR2 serve as a gate-keeper of MET activity in glioblastoma cells but not, as far as is known, in endothelial cells, which also express MET?

Furthermore, the PTP1B-mediated dephosphorylation is specific for MET and does not affect VEGFR2, even though the molecules exist in complex, implying a level of specificity that is difficult to comprehend in molecular terms. It does not seem to involve the famous VEGF coreceptor, neuropilin-1. Why, where, and how do these unconventional molecular complexes arise? Are they enriched in

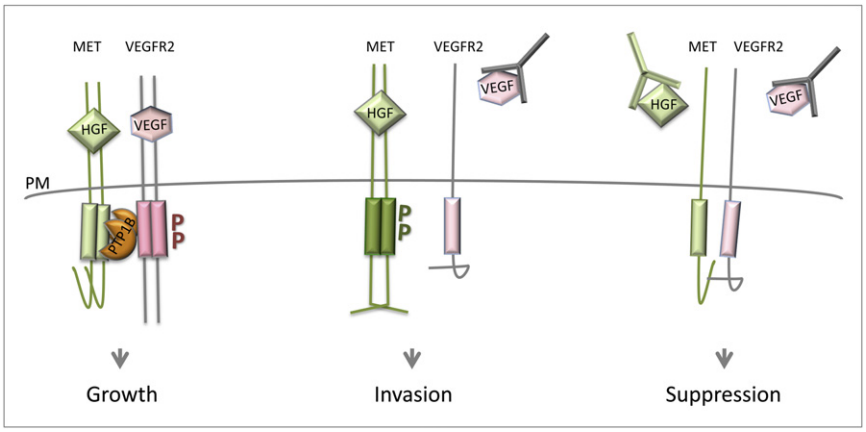

Figure 1. VEGF Suppresses MET Phosphorylation and Signaling via PTP1B
In glioblastoma cells, MET and VEGFR2 exist in a complex that also includes PTP1B, which allows growth of the tumor (left). Treatment with bevacizumab to neutralize VEGF reduces PTP1 activity and promotes MET signaling, leading to increased invasion (middle). Combined treatment to neutralize HGF and VEGF leads to efficient suppression of glioblastoma invasion (right). VEGFR2 (red) and MET (green) are indicated as monomers or dimmers, with the kinase domain shown as a rectangle, either phosphorylated (P) or not. The Pac-man symbol indicates PTP1B (orange). Intense colors indicate induction of enzymatic activities of kinases and the phosphatase. VEGF and HGF are shown either bound to their cognate receptors or as neutralized by specific antibodies against VEGF (middle) or HGF and VEGF (right). As an alternative to HGF antibodies, MET kinase inhibitors may be used clinically. PM, plasma membrane.

plasma membrane microdomains so densely packed with signal transducers that molecular interactions can occur also between unrelated receptor tyrosine kinases (Figure 1)? The interactions seem specific; at least Lu et al. (2012) could not detect any effects of PDGF and EGF on MET activity.

The study by Lu et al. (2012) has several novel implications with regard to optimization of treatment for glioblastoma multiforme and other forms of cancer. First, combined treatment with agents blocking HGF or MET in combination with bevacizumab should have the important double benefit of reducing edema and preventing invasiveness of the glioma cells. As the clinical development of efficient HRG and MET inhibitors is being actively pursued (Gherardi et al., 2012), combined treatment may be implemented very soon. Second, although there appear to be glioma-specific vascular aspects such as transdifferentiation of glioma stem cells to form vascular channels (Chamberlain, 2011), it is likely that VEGFR2 or other receptor tyrosine kinases also present PTP1B to MET in other types of malignancies. Indeed, Sennino et al. (2012) recently demonstrated that combined inhibition of MET and VEGF signaling suppresses tumor invasion and metastasis in neuroendocrine tumors in mouse models. Finally, the community is wise to expect further hurdles on the road toward efficient antiangiogenic therapy. Still, the obstacles we have encountered this far are, at least in hindsight, not very surprising, and are consistent with what we know about VEGF biology. High-quality basic research on VEGF and its mechanisms of action remains crucial for overcoming these hurdles, as demonstrated by Bergers and her colleagues.

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