Antiangiogenic treatments targeting vascular endothelial growth factor (VEGF) signaling have led to both progression-free and overall survival benefits for patients with recurrent glioblastoma (1, 2). Preclinical and clinical studies suggest that alleviation of brain edema is primarily responsible for these promising results (2, 3). Several potential biomarkers indicating benefit from or resistance to anti-VEGF therapy have also been proposed (4). For example, the angiopoietin (Ang)-1/Ang-2 ratio correlates with survival (5) and vascular normalization of glioblastoma patients (6), whereas high Ang-2 levels correlate with resistance to anti-VEGF therapy (6). VEGF and Ang-2 are strongly induced by hypoxia in tumors. The induced Ang-2 destabilizes mature vessels, enabling VEGF to promote angiogenesis. A subsequent increase in Ang-1 levels and a decrease in Ang-2 levels stabilize the newly formed vessels. This concerted action of VEGF (7) and Ang/Tie-2 signaling also regulates vascular permeability. Induction of Ang-2 in tumor vessels not only increases permeability but also sensitizes endothelial cells to angiogenic or antiangiogenic stimuli by destabilizing vessels (8). Therefore, depending on the microenvironment, increased Ang-2 expression can induce vessel formation or regression (Supplementary Table S1) and may affect the efficacy of anti-VEGF treatments.

Several studies have shown that a combination of VEGF-targeting agents and vessel-destabilizing agents is more effective than monotherapies for causing vessel regression and inhibiting tumor growth (9, 10). However, vessel-destabilizing agents, such as Ang-2, may create adverse effects in brain tumors in which edema is a major concern. VEGF is a direct regulator of Ang-2, and the expression of Ang-2 has been linked to the inhibition of VEGF in
Materials and Methods

Translational Relevance

Bevacizumab, an anti–vascular endothelial growth factor (VEGF) antibody, has recently been approved for the treatment of recurrent glioblastoma. However, the survival benefits from anti-VEGF treatment are modest, and additional targets for antiangiogenic treatment are urgently needed for recurrent glioblastoma. In glioblastoma patients, angiopoietin (Ang)-2 levels correlate with survival and are associated with tumor vascular normalization and resistance to anti-VEGF therapy. However, the effects of Ang-2 in the context of anti-VEGF treatment have not been explored in glioblastoma. Here, we investigated the role of Ang-2 during anti-VEGF treatment and found that high levels of Ang-2 interfered with vascular normalization induced by VEGFR2 inhibition; this compromised the survival benefits of anti-VEGF2 treatment. Our findings imply that the efficacy of anti-VEGF therapy can be compromised if Ang-2 levels are high. Thus, Ang-2 inhibition is a worthwhile addition for improving the outcome of current anti-VEGF therapies.

Tumor model

Human Ang-2 was cloned into the retroviral vector pBMNIGFP, and retroviral particles were packaged in colorectal cancer patients (11). In recurrent glioblastoma patients, blockade of VEGF signaling with the VEGF receptor tyrosine kinase inhibitor cediranib significantly reduced levels of plasma Ang-2 in some patients. However, this decrease was transient and modest (6), and its implications for anti-VEGF therapy remain unknown. In contrast to modest regulation of Ang-2 and the small benefit from anti-VEGF treatments in glioblastoma patients, VEGF receptor 2 (VEGFR2) blockade in our mouse glioma model was very effective at Ang-2 down-regulation and conferred significant survival benefit. This sharp contrast in responsiveness to anti-VEGF treatments between glioblastoma patients and our mouse glioma model, together with the correlation between Ang-2 levels and tumor progression in patients led us to hypothesize that Ang-2 regulation by anti-VEGF treatment contributes to the efficacy of anti-VEGF therapies.

To investigate the potential role of Ang-2 during anti-VEGFR2 treatment, we ectopically expressed Ang-2 in an orthotopic glioma model, mimicking regulation of Ang-2 seen in human glioma patients. We found that high levels of Ang-2 by ectopic expression destabilized vessels, interfered with vascular normalization by VEGFR2 inhibition, and compromised the survival benefits of anti-VEGFR2 treatment.

Tumor growth and survival

Tumors implanted in cranial windows were imaged using Zeiss Axiosplan intravital fluorescence microscopy (Zeiss), and tumor volume was calculated using the formula: Volume = 0.5 × Longer length × Shorter length². Control rat IgG or DC101 (anti-VEGFR2 antibody, ImClone Systems) was i.p. injected every 3 days (40 mg/kg body weight). For Tie-2 inhibition, 10⁷ pfu of AdExTek (a gift from Dr. Charles Lin, Vanderbilt University; ref. 12) or AdLacZ virus were i.v. injected 24 hours before DC101 or IgG treatment. Survival experiments were terminated when mice became moribund or lost >20% of body weight or showed sign of paralysis.

Quantitative reverse transcriptase-PCR

Total RNA extraction from tumor tissues was done with TRizol reagent (Invitrogen) according to the manufacturer’s instructions. RNA was further purified with RNeasy Mini kit (QIAGEN). cDNAs were synthesized using Taqman reverse transcription kit (Applied Biosystems) and specific primers. Primers sequences used were: mouse Ang-2 (forward) 5′ GCATGACCTAATGGAGACCGTC3′, (reverse) 5′ GATAGCAACCGAGCTCTTGGAG 3′; mouse VE-cadherin (forward) GCCTCACGTCAAGGTGCATGA 3′, (reverse) 5′ ATCCTGGCCACAGATGGCCTTG 3′; mouse Gapdh (forward) 5′AAGAAAGGTGTGAGAACGCGAGA 3′, (reverse) 5′ TGCTGTGTGACTCAGAGGAGA 3′.

Permeability and RBC velocity

The tumor area was localized by GFP signal constitutively expressed by U87 and U87-Ang2. Two adjacent areas were imaged by intravital multiphoton laser scanning microscopy (MPLSM) and three-dimensional image stacks were acquired (3).

Vessel permeability to bovine serum albumin (BSA) was determined after i.v. injection of 0.1 mL (5 mg/ mL) TAMRA-BSA or Alexa647-BSA (Invitrogen) as described previously (3). We alternated the use of TAMRA and Alexa647-conjugated BSA to minimize the residual background fluorescence. Ten minutes after i.v. injection
of BSA, Z stack images of 200 μm with 2.5 μm intervals were collected every 3 to 4 minutes up to 60 minutes. The increase in extravasated fluorescence dye intensity was normalized by blood vessel surface area. For RBC velocity analysis, we labeled RBCs ex vivo with a far-red lipophilic fluorescent dye [1,1′-dioctadecyl-3,3,3′,3′-tetramethylindodicarbocyanine perchlorate (DiD); Invitrogen], allowing observation deep inside the tissue via MPLSM. The labeled RBCs were mixed with the endogenous mouse blood via systemic injection at a ratio of 3 to 5 labeled RBCs per 100. Line scanning was done using MPLSM to determine RBC velocity. All image analysis was completed using an in-house algorithm (MATLAB, Mathworks; ref. 13). For more details of the data analysis, see Supplementary Methods.

Magnetic resonance imaging
All magnetic resonance images were acquired using a 9.4 Tesla MRI scanner (Bruker Biospin). Animals were anesthetized with a 50:50 mixture of O2 and medical air plus 1.5% isofluorane and placed prone in a homebuilt cradle. A custom-built transmit-receive birdcage mouse-head coil was used to acquire the images. T2 relaxation maps were generated from multi-echo spin-echo images and used to assess tumor edema. Acquisition parameters were: TE, 10 ms; 10 echoes; TR, 2,500 ms; 11 image slices; 0.5 mm slice thickness; 150 μm in-plane resolution; NA, 2. Voxelwise exponential fitting of the image signal intensity as a function of echo-time was done using a MATLAB program written in-house to determine T2 relaxation time maps.

Immunohistochemistry and Western blot analysis
To label the perfused blood vessels, 100 μg of biotinylated Lycopersicon Esculentum (Tomato) Lectin (Vector Laboratory) were i.v. injected into mice, followed by perfusion fixation with 4% formaldehyde. Frozen tissue sections (20 μm thick) were blocked in 5% non-fat milk in PBS with 0.1% Triton X-100 and stained with Alexa 647-conjugated streptavidin (1:200, S21374, Invitrogen). Pericytes were stained with Cy3-conjugated anti-α smooth muscle actin (αSMA) antibody (1:200, C6198, Sigma) or anti-NG2 antibody (1:200, AB5320, Millipore). Ang-2 staining was done using polyclonal anti-Ang-2 antibody (1:100, AF623, R&D Systems) after heat retrieval at 95°C for 5 minutes in target retrieval solution (S1699, DAKO). Images of four different fields per tumor section were collected with Olympus laser scanning microscope using 20× objective lens. Quantification of the stained area was done using our in-house segmentation algorithm (MATLAB, Mathworks). Image analysis was done as previously described (3). Images were processed using Adobe Photoshop CS3 software (Adobe Systems Inc.).
Soluble Tie-2 expression was determined by Western blot analysis. Plasma samples (3 μL each) from mice were separated on 8% denaturing polyacrylamide gel and transferred to polyvinylidene difluoride membrane. The membrane was incubated with polyclonal anti-Tie-2 antibody (1:1,000, AF313, R&D Systems), followed by horseradish peroxidase-conjugated donkey anti-rabbit IgG (1:5,000, NA934V, GE Healthcare). The membrane was incubated in enhanced chemiluminescence (ECL) plus detection reagent (RPN2132, GE Healthcare) and exposed to Kodak ML film.

Data collection and statistical analysis
Data are expressed as mean ± SE. Student’s t-test (two-tailed with unequal variance) was done for statistical analysis using Microsoft Excel software. The Kaplan-Meier method was used for survival studies. We considered \( P < 0.05 \) to be statistically significant. For survival, permeability, and magnetic resonance imaging (MRI) studies, all data from multiple experiments were combined, analyzed, and presented. Other studies were repeated at least three times and representative data were presented.

Results

**Anti-VEGFR2 treatment transiently reduces Ang-2 expression**

We first determined the kinetics of Ang-2 expression during anti-VEGFR2 treatment. Ang-2 was predominantly expressed in tumor blood vessels of glioma xenografts (Fig. 1A) similar to patterns seen in autopsy samples from patients (14). Because Ang-2 was mainly expressed in vascular endothelial cells, we normalized the expression level of Ang-2 with respect to the endothelial cell specific marker VE-Cadherin. As shown in Fig. 1B, DC101 treatment significantly, but transiently, reduced Ang-2 levels at day 2 followed by a gradual increase at later time points.

![Fig. 2. The effect of Ang-2 and VEGFR-2 inhibition on tumor growth and survival. A, tumor-bearing mice were treated with IgG (dotted line) or DC101 (solid line) and followed for their survival. DC101 treatment significantly extended mice survival and Ang-2 compromised the survival benefit of DC101. B, DC101-treated mice (filled circle) survived with significantly larger tumors compared with untreated mice (open circle), but not Ang-2 tumor-bearing mice. C, neither Ang-2 nor DC101 treatment had an effect on tumor growth. Dotted and solid lines, IgG and DC101 treatments, respectively. Each line represents an individual mouse.](#)
Ang-2 compromises the survival benefit from anti-VEGF therapy

To investigate the potential role of Ang-2 during anti-VEGF therapy, we ectopically expressed Ang-2 in glioma cells (U87-Ang-2) to maintain high Ang-2 levels during DC101 treatment (Supplementary Fig. S1A). Testing for potential autocrine effects, we found that ectopic expression of Ang-2 did not affect growth of the cancer cells in vitro (Supplementary Fig. S1B). Also, there were no significant changes in the expression of angiogenesis genes as determined by an angiogenesis PCR array (SABiosciences; Supplementary Table S3).

Next, we determined if Ang-2 expression or DC101 treatment affects tumor growth and animal survival. DC101 treatment significantly extended survival of glioma-bearing animals (Fig. 2A). Interestingly, tumor size at the end point was significantly larger in DC101-treated U87 tumors compared with control IgG-treated tumors, suggesting that DC101 treatment contributes to longer animal survival by reducing edema-associated mass effects (Fig. 2B). In fact, DC101 had no effect on tumor growth (Fig. 2C). These findings are consistent with our previous study with cediranib (a VEGF receptor tyrosine kinase inhibitor) treatment in this model (3).

Next, we determined the impact of Ang-2 on U87 tumor growth and survival with and without DC101 treatment. Ectopic expression of Ang-2 did not induce a tumor growth delay or affect survival of tumor-bearing mice (Fig. 2A and C). However, Ang-2 expression significantly reduced the survival benefit from DC101 (Fig. 2A). Ang-2 increased morbidity at a smaller tumor burden without affecting tumor growth (Fig. 2B and C).

Ang-2 impedes vascular normalization by anti-VEGF2 treatment

Because anti-VEGF treatment can alleviate brain tumor edema and Ang-2 is also known to regulate vascular permeability, we measured permeability in tumor vessels to

![Fig. 3. Permeability changes in tumor vasculature by Ang-2 and VEGFR2 inhibition. A, DC101 treatment decreased vascular permeability temporarily in control tumors; n = 8 (Ig G) and 9 (DC101). B, Ang-2 interfered with the effect of DC101 on vascular permeability. DC101 treatment did not reduce the vascular permeability in U87-Ang-2 tumors; n = 7 (IgG) and 8 (DC101). C, MRI was done before (day 0) and 2 days (day 2) after treatment with IgG or DC101. Representative T2-weighted images are shown. Arrows, tumors grown in cranial windows; scale bar, 2 mm. D, DC101 treatment was more effective in reducing tumor edema in U87 tumors than in U87Ang-2 tumors; n = 7.](image-url)
determine if edema contributes to the poor outcome in U87-Ang-2 tumors. Ang-2 expression alone did not change vascular permeability despite lower α-SMA-positive mural cell coverage, indicating that VEGF signaling is the dominant regulator of vascular permeability in these tumors (Fig. 3A and B). DC101 treatment significantly reduced permeability in U87 tumors at day 2 (Fig. 3A) but did not reduce permeability in U87-Ang-2 tumors (Fig. 3B). MRI confirmed that Ang-2 interfered with edema control by DC101 treatment (Fig. 3C and D). Importantly, vascular permeability positively correlated with the level of Ang-2 expression (Figs. 1B and 3A). These data indicate that Ang-2 maintained vascular leakage during DC101 treatment, leading to additional tumor mass effects and morbidity in mice with smaller tumor burden.

To further characterize the impact of Ang-2 on tumor vessel function, we measured RBC velocity. Following DC101 treatment, the mean RBC velocity in U87 tumors increased at day 2, suggesting that DC101 normalizes tumor vessels and improves their function (Fig. 4A). On the other hand, DC101 did not change mean RBC velocity in U87-Ang-2 tumors, indicating that Ang-2 interferes with vascular normalization (Fig. 4B).

Next, we evaluated the morphologic changes induced by Ang-2. Ectopic expression of Ang-2 resulted in dilated vessels (Fig. 5A), higher vessel density (Fig. 5B), and reduced mural cell coverage in U87-Ang-2 tumors (Fig. 5C, D, and E). DC101 treatment effectively reduced vessel density in both U87 and U87-Ang-2 tumors, but U87-Ang-2 tumors consistently had higher vessel density than U87 tumors, even with DC101 treatment. We also found a gradual increase in mural cell coverage during DC101 treatment in U87 tumors but not in U87-Ang-2 tumors (Fig. 5D and E), consistent with the functional data showing that Ang-2 inhibits vessel normalization by VEGFR2 blockade. Interestingly, ectopic expression of Ang-2 did not increase vessel regression by DC101 treatment despite the decrease in mural cell coverage (Fig. 5D and E), suggesting that Ang-2 did not sensitize blood vessels to VEGFR2 inhibition in this model.

Collectively, our data suggest that the decrease in Ang-2 expression after DC101 treatment is critical for structural and functional vascular normalization.

Ang-2 does not antagonize Ang-1 in glioblastoma
Because vessel function depends on the balance of Ang-1 and Ang-2 signaling through Tie-2, it is possible that Ang-2 interferes with DC101 by preventing Ang-1 from sending stabilizing signals through Tie-2. Another possibility is that Ang-2, by itself, signals for destabilization through Tie-2. To investigate this, we systemically expressed soluble Tie-2 (sTie-2) to block all signaling through Tie-2 (via both Ang-1 and Ang-2). sTie-2 expression reached a plateau within 24 hours and remained stable for at least 14 days after AdExTek administration (Fig. 6A). sTie-2 had no significant effect on tumor growth (Fig. 6B) or animal survival (Fig. 6C). Surprisingly, sTie-2 also had no significant effect on the survival benefit

Fig. 4. Effect of Ang-2 and VEGFR2 blockade on RBC velocity. A, average RBC velocity was temporally increased by DC101 treatment in control tumors. The regulation kinetics of RBC velocity correlated with kinetics of vascular permeability and Ang-2 expression. **P = 0.1. B, DC101 treatment had no effect on RBC velocity in U87-Ang-2 tumors. Left, average velocity data; right, data from individual animals; n = 5.
from DC101 treatment, suggesting that stabilizing Ang-1 signals do not contribute. Thus, the regulation of vascular permeability by Ang-2 may involve direct signaling rather than passive interference with Ang1/Tie-2 signaling. In fact, Ang-2 has been shown to increase permeability in cultured endothelial cells in the absence of Ang-1 or VEGF (15).

**Discussion**

In this work, we evaluated the potential of Ang-2 as a therapeutic target for improving anti-VEGF treatments. We found that high levels of Ang-2 limit the survival benefit from anti-VEGF therapy by interfering with edema control and vessel normalization. Brain edema is the most

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**Fig. 5.** Effect of Ang-2 and VEGFR2 blockage on tumor blood vessels. A, tumor vasculature was imaged using MPLSM after the injection of rhodamine-conjugated dextran and DiD-labeled RBC. Green, perfused vessels with rhodamine conjugated vessel; red, labeled RBCs. Vessels were dilated in U87-Ang-2 tumors compared with control tumor vasculature. DC101 treatment had no significant effect on vessel diameter. Mean vessel diameters were determined from Z stack images collected using MPLSM. Scale bar, 200 μm. B, Ang-2 increased total vessel length. DC101 treatment was equally effective in vessel trimming in both tumors. C, immunohistochemical analysis was done and images were collected using confocal laser scanning microscopy. The representative images of blood vessels and pericyte coverage after VEGFR-2 inhibition are shown. Blood vessels and pericytes from the frozen sections were stained for lectin (green) and α-SMA (red), respectively. D, Ang-2 decreased α-SMA-positive fraction in vessels. DC101 treatment increased α-SMA-positive cell coverage in control tumors but not in U87-Ang-2 tumors. E, Ang-2 had no effect on NG-2-positive fraction while interfering with the increase in NG-2-positive vessel fraction by DC101 treatment. DC101 treatment increased α-SMA-positive cell coverage only in control tumors; n = 8 (days 0 and 2) and 4 (day 8). *P <0.05.
critical complication of brain tumors, and the benefits of antiangiogenic treatment seem to be primarily through relieving brain edema (3, 6). Thus, our results suggest that Ang-2 inhibition in combination with an anti-VEGF agent may be a good strategy for controlling edema associated with brain tumors. Of note, Ang-2 levels have been shown to correlate with vascular leak syndrome in high-dose interleukin-2 treatment of patients with metastatic renal cell carcinoma and melanoma (16). Along these lines, dexamethasone, a commonly used steroidal drug to control brain edema, is known to suppress Ang-2 and VEGF expression (17, 18).

Ang-2 expression is mainly associated with endothelial cells in our tumor model as well as in glioblastoma autopsy tissue (data not shown). Because we ectopically expressed Ang-2 in tumor cells in this study, it is possible that our tumor model does not completely reproduce human brain tumor biology. However, because Ang-2 is known to be readily diffusible and we did not detect any autocrine effect of Ang-2 on tumor cells, we suggest that tumor-expressed Ang-2 is an acceptable substitute for endothelial cell–derived Ang-2.

We found that Ang-2 increased tumor angiogenesis but did not affect the antiangiogenic efficacy of a VEGFR2 inhibitor. Extensive vessel pruning by anti-VEGFR2 treatment did not slow tumor growth, suggesting that the remaining tumor vessels were sufficient to support tumor growth (3, 19). It should be noted, however, that the effects of ectopic expression of Ang-2 on tumor growth and angiogenesis depend on tumor cell type and tumor site (Supplementary Table S1). This may be attributed to autocrine effects on tumor cells, endogenous levels of Ang-1, or other factors. Interestingly, Nasarre et al. reported that host-derived Ang-2 affects early stages of tumor development and vessel maturation but is dispensable at later stages of tumor growth (20). These results may explain why Ang-2 had no effect on tumor growth in our tumor model (Fig. 2), as we used fully established tumors in our study. On the other hand, similar to previous reports (21–23), we noticed a growth delay in U87Ang-2 tumors when we used cell suspension for tumor implantation (data not shown).

Using intravital imaging, we found that anti-VEGFR2 treatment functionally normalized tumor blood vessels, as shown by reduced vascular permeability and increased RBC velocity, and Ang-2 compromised the vessel normalizing effect of anti-VEGFR2 treatment. These data confirm previous findings that Ang-2 destabilizes tumor vessels and promotes angiogenesis, whereas Ang-2 inhibition normalizes tumor vessels (24). However, Ang-2–mediated vessel destabilization did not increase the antiangiogenic efficacy of DC101. In U87 tumors, DC101 treatment resulted in a gradual increase in mural cell coverage, but changes in vessel function, i.e., permeability and mean
RBC velocity, were temporary. In addition, tumor size did not reflect the benefit of treatment in brain tumors (3). Collectively, our results underscore the importance of functional measurements in evaluating the efficacy of any treatment in glioblastomas.

As in our tumor model, Ang-2 was transiently reduced in glioblastoma patients after antiangiogenic treatment (Fig. 1A). One potential mechanism of transient nature of this decrease is the induction of Ang-2 by hypoxia caused by excessive vascular pruning. We tested this hypothesis by determining the expression of hypoxia-responsive genes. However, the hypoxia-responsive genes, such as CA9 and LOX, were not affected by DC101 treatment, suggesting that hypoxia is not the direct cause of Ang-2 regulation by anti-VEGF2 treatment (Supplementary Fig. S2A). Recently, granulocyte colony-stimulating factor (G-CSF) has been shown to be induced by vascular disrupting agents and to mediate the resistance to antiangiogenic therapy (25, 26). G-CSF also has the potential to induce Ang-2 expression (27). However, there was no significant change in G-CSF levels after DC101 treatment (Supplementary Fig. S2B). DC101 treatment increased mural cell coverage of tumor vessels, which could render the endothelium resistant to antiangiogenic treatment. It is, therefore, possible that vessels inherently resistant to DC101 treatment and mature vessels that survived during DC101 treatment continue to produce Ang-2 in a VEGFR2-independent manner, which could be a potential bounce-back mechanism of Ang-2 expression during DC101 treatment.

The important implication of our study is that in tumors where Ang-2 levels remain high during anti-VEGF treatment, the efficacy of anti-VEGF therapy might be limited. Therefore, the modest reduction of Ang-2 seen in glioblastoma patients treated with cediranib might partly account for the limited efficacy of anti-VEGF therapy. Our findings support the recent studies, done in ectopic tumor xenograft models, suggesting that Ang-2 is a viable therapeutic target (Supplementary Table S2) and that simultaneous inhibition of VEGF and Ang-2 pathways is more effective than inhibition of either pathway (28).

Disclosure of Potential Conflicts of Interest

R.K. Jain: commercial research grant, AstraZeneca and Dyax; honoraria from speakers bureau, Aplylam, Pfizer, and Genzyme; consultant/advisory board, AstarZeneca, Takeda-Millenium, Dyax, Genzyme, Morphosys, Regeneron, and SynDevRx; A.G. Sorensen: commercial research grant, AstraZeneca, Medical Solutions and Siemens; consultant/advisory board, ACRIN, Genentech, Regeneron, Millenium Pharmaceuticals, Novartis, Mitsubishi, and Biogen.

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Angiopoietin-2 Interferes with Anti-VEGFR2–Induced Vessel Normalization and Survival Benefit in Mice Bearing Gliomas
