Vascular Endothelial Growth Factor-Trap Decreases Tumor Burden, Inhibits Ascites, and Causes Dramatic Vascular Remodeling in an Ovarian Cancer Model

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ABSTRACT
Ovarian cancer is the most lethal gynecological malignancy and the fifth most common cause of cancer in women. It is characterized by diffuse peritoneal carcinomatosis and often by large volumes of i.p. ascites. Because vascular endothelial growth factor (VEGF), also known as vascular permeability factor, increases vascular permeability and stimulates endothelial cell growth, its role in ovarian cancer has been evaluated in a number of studies. However, questions remain regarding the ability of VEGF alone to cause ascites formation and the ability of VEGF blockade to inhibit the growth of disseminated cancer. We have used retroviral technology to create cell populations that overproduce VEGF and report that enforced expression of VEGF by ovarian carcinoma cells dramatically reduces the time to onset of ascites formation. In fact, even tumor-free peritoneal overexpression of VEGF, created by using adenoviral vectors, is sufficient to cause ascites to accumulate. We have found that systemic administration of the VEGF-Trap, a recently described high-affinity soluble decoy receptor for VEGF, prevents ascites accumulation and also inhibits the growth of disseminated cancer. Remarkably, much as is observed in s.c. tumor models, VEGF blockade results in dramatic remodeling of the blood vessels in disseminated ovarian carcinoma. The potent effects of the VEGF-Trap in reducing both ascites and tumor burden suggest that it will be of value in a regimen for treatment of women with ovarian cancer and ascites.

INTRODUCTION
Angiogenesis, the development of new capillaries from existing vasculature, is an important component of tumor growth because many types of tumors are associated with growing blood vessels, whereas others cannot grow more than 2–3 mm without developing a new blood supply (1). VEGF5 is a potent angiogenic factor whose receptors, including VEGFR-1 (Flt-1) and VEGFR-2 (KDR/Flk-1), are selectively located on vascular endothelial cells. By activating its receptors, VEGF, which also is known as vascular permeability factor, both exerts a mitogenic effect on endothelial cells (2–5) and increases vessel permeability (6, 7). It is expressed in increased amounts in ovarian cancers and other solid tumors (8–14). Although the value of quantifying serum levels of VEGF as a prognostic indicator of ovarian cancer is unclear (15–22), substantial evidence suggests that VEGF promotes the formation of ascites. It is present at very high levels in the ascites of patients with advanced ovarian cancer and is similarly present in animals inoculated with human ovarian tumor cells; furthermore, VEGF blockade in animal models dramatically reduces ascites formation (23–30).

Previously, we and others have found that VEGF blockade inhibits ascites formation in a SKOV-3 ovarian carcinoma model. Unfortunately, due to the dispersion and invasiveness of the tumor cells in this model, tumor burden was difficult to evaluate, and we could not demonstrate significant, reproducible decreases in tumor burden (28). In similar models, however, less specific tyrosine kinase inhibitors have been shown to decrease tumor burden (31–33), raising the question of whether VEGF blockade on its own is inadequate to block tumor growth, or whether VEGF-specific blocking agents tested to date have lacked potency. When considering the therapeutic potential of VEGF blockade in ovarian cancer, it is important to distinguish whether VEGF blockade alone has the potential to reduce both ascites formation and tumor burden, or whether it will block only ascites formation (suggesting that the success of tyrosine kinase inhibitors is attributable to their ability to block multiple kinases). Because resolving this question may provide guidance in planning future clinical trials, we felt additional studies with a potent, yet specific, VEGF blocking agent were warranted.

We designed the present studies to further substantiate that

Received 5/7/03; revised 8/1/03; accepted 8/5/03.
Grant support: Supported, in part, by National Cancer Institute SPORE grant CA083639.
The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
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3 The abbreviations used are: VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor; MCS, multi-cloning site; GFP, enhanced green fluorescent protein; mVEGF, mouse VEGF; FACS, fluorescence-activated cell sorting.
VEGF plays a role in both the formation of ascites and growth of ovarian cancer and to assess changes in tumor vasculature after VEGF blockade. Because tumor burden itself may contribute to ascites formation, viral technologies were used to assess the ability of VEGF to cause ascites formation in both tumor-bearing and tumor-free mice. Retroviruses were used to engineer a population of human SKOV3 carcinoma cells to over-produce mVEGF (the mouse gene was used so that the expression of the transduced gene could be discriminated from that of endogenous VEGF), whereas adenoviruses were used to directly transduce the cells of the peritoneum to produce VEGF. After establishing that VEGF itself was sufficient to promote ascites formation, we then explored the effects of VEGF blockade in both the SKOV-3 model and a second model using OVCAR-3 cells. The OVCAR-3 model has proven to be more appropriate for assessing effects on ascites and tumor burden (32, 33), and it was also used to assess changes in tumor vasculature after VEGF blockade.

To block VEGF, we used the VEGF-Trap, a recently described high-affinity soluble decoy receptor that comprises portions of the extracellular domains of both VEGFR-1 and VEGFR-2. This composite decoy receptor has low picomolar affinity for both mouse and human VEGF, as well as an extended half-life in vivo (34, 35); thus, it acts as a potent inhibitor of tumor- and host-derived VEGF (34, 35). The VEGF-Trap is more specific than kinase inhibitors, but unlike monoclonal antibodies to VEGF, it does not discriminate between VEGF produced by different animal species.

Here we report that inactivation of VEGF, using the VEGF-Trap, inhibits ascites formation in both models and significantly reduces tumor burden in the OVCAR-3 mouse model. Remarkably, the changes in vascular architecture evoked by the VEGF-Trap in disseminated ovarian cancer are strikingly similar to those observed in s.c. grown tumor cells of different origin.

**MATERIALS AND METHODS**

**Materials.** VEGF-Trap (34, 35) vehicle and human Fc control were from Regeneron Pharmaceuticals (Tarrytown, NY).

**Cell Lines.** Ascites fluid from athymic mice previously inoculated with OVCAR-3 cells was kindly provided by Dr T. Hamilton (Fox Chase Cancer Center, Philadelphia, PA). Cells from the SKOV-3 human cystadenocarcinoma cell line, obtained from American Type Culture Collection (Manassas, VA), were grown in McCoy’s 5a medium with 1.5 mM l-glutamine, penicillin, and streptomycin, supplemented with 10% FCS. Cells were grown to confluence and harvested by trypsinization with 0.25 mg/ml trypsin/EDTA before injection.

**Animals.** Thirty-six athymic Balb/c nu/nu mice (Simon- sen Laboratories, Gilroy, CA) were housed in isolated conditions in the University of California, San Francisco Laboratory Animal Resource Center. All protocols involving immunodeficient mice were approved by the Committee on Animal Care, University of California, San Francisco. Alternatively, 25 athymic Balb/c nu/nu mice (Jackson Laboratory, Bar Harbor, ME) were received at Regeneron Pharmaceuticals at 5–6 weeks of age and allowed to acclimatize for 1–2 weeks. All animals were housed under pathogen-free conditions and fed autoclaved pellets and water.

**Retroviral Constructs.** The pLZR Phoenix vector was obtained from Dr. G. Nolan (Department of Pharmacology, Microbiology and Immunology, Stanford University) and modified by the addition of a MCS followed by an internal ribosome entry sequence-GFP cassette (36). Thus, genes subcloned into the MCS produce bicistronic constructs under the control of the viral S’ long terminal repeat. The entire coding sequence of mVEGF, was inserted into the MCS for the construct used to transduce cells with VEGF, whereas the MCS was left empty for the GFP-only vector. Constructs were transfected into Amphotropic packaging lines to produce infective virus using standard techniques (37).

**SKOV-3 Model.** SKOV-3 cell lines were infected with Amphotropic viruses encoding either mVEGF, and GFP or GFP only. Cells that were successfully transduced with the retroviruses were collected by FACS using a Cytomation MoFlo (Fort Collins, CO) with fluorescence emission from GFP measured with a 530/540 nm bandpass filter. More than 50% of the cells were GFP positive after infection, allowing >4.0 × 10^5 cells to be collected and used to establish cell lines. To verify viral transduction, cells were sorted several days later and found to be >80% positive for GFP expression. Cells were then expanded, aliquoted, and frozen. All experiments were performed with an aliquot expanded by 4–5 passages and tested for viability before injection.

**In Vivo Adenoviral and SKOV-3 Studies.** Adenoviral constructs have been described previously (38). Adenoviral plaque-forming units (5.0 × 10^9) or 1.0 × 10^7 SKOV-3 cells were suspended in a volume of 300–400 μl of PBS or serum-free cell culture medium and injected i.p. into female nude mice. VEGF-Trap or control buffer was delivered twice weekly at 25 mg/kg via s.c. injection in a volume of 50–200 μl. Mice were assessed daily for general health and development of ascites and weighed at least twice weekly. Animals were sacrificed if they had lost >10% of body weight or had persistent ascites on three consecutive assessments. After sacrifice, ascites was removed with a sterile thin caliber plastic transfer pipette and quantified, and hematocrit was measured.

**OVCAR-3 Model.** OVCAR-3 cells obtained from ascites fluid were prepared as described previously (32, 33). Briefly, 2 × 10^6 cells in 500 μl of RPMI 1640 were injected i.p. into athymic Balb/C nude (nu/nu) mice. Fourteen days after inoculation, blinded administration of VEGF-Trap or human Fc as control was initiated at a dose of 25 mg/kg, based on previous experiments (34). Injections were given s.c. in the nape of the neck using a 28.5-gauge needle and a 0.5-ml insulin syringe. Injections (0.05 ml) were administered twice weekly throughout the experimental period. Body weight and abdominal circumference were quantified twice weekly. In addition, animals were monitored daily for evidence of advanced disease (listlessness, extensive swelling of the abdominal cavity). During the experimental period, seven mice in the control group underwent euthanasia prematurely as a result of extensive disease. At the same time, sister mice in the other group also underwent euthanasia so that appropriate comparisons could be made. At the end of the experiment, all remaining mice underwent euthanasia with CO₂ followed by cervical dislocation. The volume of
ascites was measured, and tumors were excised and weighed. Immediately before sacrifice, mice received i.v. injection with FITC lycopersicon lectin (see below).

**Tumor Vasculature.** s.c. tumors were established as described previously (34). After small s.c. tumors became palpable (1 week after implantation), treatment with the VEGF-Trap was initiated. VEGF-Trap or an equivalent volume of vehicle was delivered twice weekly s.c. at the nape of the neck. Tumor vasculature was visualized by using antibodies to platelet-endothelial cell adhesion molecule for immunohistochemistry as described previously (34).

VEGF-Trap-treated OVCAR-3 tumor-bearing mice and control, untreated tumor-bearing mice were anesthetized by i.m. injection with ketamine (87 mg/kg; Sanofi Winthrop Pharmaceuticals, New York, NY) and xylazine (13 mg/kg; Phoenix Pharmaceuticals One, St. Joseph, MI), followed by i.v. injection with 100 μl of FITC lycopersicon lectin or 100 μg of Cy3 albumin (Jackson Immunology Research, West Grove, PA). Ten min later, mice were perfused through the ascending aorta with 4% paraformaldehyde in PBS for 2 min. Tumors and control organs were extracted and placed in fixative for 1–2 h followed by immersion in 30% sucrose/PBS overnight, embedded in OCT, cryostat sectioned, and viewed by fluorescence microscopy.

**RESULTS**

**Ascites Formation Is Accelerated by VEGF Overexpression and Can Be Blocked Using VEGF-Trap.** We have previously described a SKOV-3 model of ovarian carcinoma (28). To produce a more rapid model of ascites and to support the hypothesis that VEGF is the major causative agent in ascites (28), to produce a more rapid model of ascites and to support the hypothesis that VEGF is the major causative agent in ascites (28), we have collected by FACS; analysis by ELISA demonstrated that, highest levels of fluorescent GFP reporter (Fig. 1 using these retroviral vectors, cell pools that expressed the vector that produces VEGF as well as GFP. After infection control vector was generated that expresses only GFP, as was a to overexpress mVEGF using retroviral vector technology. A secondary to ovarian carcinoma, SKOV-3 cells were engineered the hypothesis that VEGF is the major causative agent in ascites (28). To produce a more rapid model of ascites and to support previously described a SKOV-3 model of ovarian carcinoma (28). To produce a more rapid model of ascites and to support the hypothesis that VEGF is the major causative agent in ascites (28).

To determine hematocrit. n.d. = not done, because there was insufficient accumulation of ascites in this group of animals to determine hematocrit. n = 10 for studies using SKOV-GFP cells, and n = 15 for studies using SKOV-VEGF cells.

**Fig. 1.** A. SKOV-3 cells were transduced to express either GFP or mVEGF<sub>164</sub> and GFP using retroviruses as described. The use of retroviruses allowed large cell populations to be transduced with the gene of interest. Because retroviral constructs all contained an internal ribosome entry sequence-GFP, infected populations of cells were highly fluorescent, as can be seen by the peaks of cells shifted to the right along the X axis (f11), and they could be separated easily by FACS. Populations consisting of >4.0 × 10<sup>5</sup> cells (as shown by the R2 gate) were collected and plated after sorting. This population was then resorted to ensure stable viral uptake. B. When tumor cells were implanted i.p. in nude mice, enforced expression of VEGF resulted in earlier onset of ascites formation; however, the hematocrit of the ascites was similar in mice bearing GFP- or VEGF-transduced cells. Treatment with VEGF-Trap either the day after tumor cell inoculation (SKOV-VEGF) or 2 weeks after tumor cell inoculation (SKOV-GFP) dramatically delayed the onset of ascites formation; when ascites did form, the volume was markedly reduced, as was the hematocrit (n.d. = not done, because there was insufficient accumulation of ascites in this group of animals to determine hematocrit). n = 10 for studies using SKOV-GFP cells, and n = 15 for studies using SKOV-VEGF cells.

well as to evaluate the utility of the VEGF-Trap, mice inoculated with either of these cell populations were treated with twice weekly doses of 25 mg/kg VEGF-Trap. Because the onset of ascites is more rapid in the SKOV-VEGF-inoculated animals, treatment with VEGF-Trap was initiated 1 day after tumor cell implantation, whereas treatment of mice inoculated with SKOV-GFP cells was not started until 14 days after tumor implantation. Most mice that were treated with the VEGF-Trap did not develop ascites in the timeframe tested, and those that did develop ascites exhibited much lower volumes. In addition, the ascites was markedly less hemorrhagic on VEGF-Trap treatment.
Enforced VEGF Overexpression in the Peritoneum Using Adenoviral Vectors, in the Absence of Tumor Cells, Is Sufficient to Promote Ascites Formation. The above studies confirmed the requirement for VEGF in a tumor-induced ascites model but did not address whether VEGF overexpression itself might be sufficient to induce ascites in the absence of peritoneal invasion by tumor. To evaluate this, $5 \times 10^8$ plaque-forming units of replication-deficient adenoviruses encoding mVEGF$_{165}$ or GFP (37), were injected into the peritoneum of female nude mice. Rapid accumulation of ascites on days 3–4 after injection was observed in 100% of mice injected with the VEGF-encoding viruses, but not in any animals injected with the control virus. Ascites fluid was hemorrhagic, and hematocrit of ascites fluid measured $\pm 20 \pm 4\%$.

Effects of VEGF-Trap in OVCAR-3 Ovarian Cancer Model: Inhibition of Tumor Growth as well as Ascites. To examine the effects of the VEGF-Trap on tumor growth as well as ascites, we used a model of i.p. ovarian carcinoma in athymic immuno deficient mice that was developed in our laboratory (28) using the OVCAR-3 cell line (32, 33). Because tumor growth is more restricted to easily identifiable surfaces rather than to mesentery and fascia, as occurs in the SKOV model, it is much easier to estimate tumor burden in this model. In addition, in the OVCAR-3 model, ascites develops earlier in the progression of the disease than in the SKOV-3 model, in which it is a near terminal event. This permits more accurate quantification of treatment effects on ascites.

In all animals treated (control, $n = 18$; VEGF-Trap, $n = 18$, three subgroups of 6 mice/group), s.c. injections were initiated 14 days after OVCAR-3 cell inoculation and continued for 5 weeks. At postmortem examination, tumors were found on the surface of the peritoneum and uterus in both control and treated groups. However, in the control group, tumors were also found on the diaphragm, in the hilus of the liver, and on the intestines.

Because i.p. tumor growth could not be monitored directly, body weight and abdominal circumference, which reflect both increasing ascites accumulation and tumor burden, were quantified twice weekly and plotted as the weekly average measurement for each parameter (Figs. 2 and 3).

I.p. tumor burden and ascites volume were both quantified at postmortem examination. All visible i.p. tumors were excised and weighed. Mean tumor burden in the VEGF-Trap-treated group ($1.69 \pm 0.33$ g) was reduced by $56\%$ compared with the control group ($3.83 \pm 0.47$ g; $P < 0.001$; Fig. 4). Treatment with the VEGF-Trap completely inhibited measurable ascites (Fig. 5). The mean volume of ascites in the control group was $2.79 \pm 0.52$ ml.

Effects of VEGF-Trap on Tumor Vasculature: Remodeling of Vascular Architecture. Having established that VEGF blockade not only prevents ascites formation but also dramatically reduces tumor burden in the OVCAR-3 model, we examined the effects of VEGF blockade on the vascular architecture of the tumors.

Visualization of FITC lycopersicon lectin indicated a higher density and greater tortuosity of vessels surrounding tumors of untreated mice, compared with treated mice (Fig. 6, A and B). Cy3 albumin also was visualized by fluorescence microscopy. Cy3 albumin localized in liver sinusoids of both untreated and treated mice, suggesting that it is retained in vessels of some organs in both normal and tumor-bearing mice. Cy3 albumin was seen in some, but not all, tumor vessels, whereas VEGF-Trap-treated mice had very few vessels with detectable Cy3 albumin. In addition, using FITC lycopersicon, the peritoneal vessels of untreated mice had diffuse images, consistent with their being permeable to the FITC lectin, whereas those in the treated mice were noticeably less diffuse, indicating that the FITC lectin was contained within the vessels to a greater extent than in the untreated mice. The vessels in the peritoneum of normal, non-tumor-bearing control mice were sharp and well defined. To determine whether the dramatic vascular remodeling observed in this model was a consequence of the origin of the tumor cells, the vessels that supplied the tumor, or purely a consequence of VEGF withdrawal, we examined the effects of VEGF blockade on s.c.-implanted C6 glioma tumors. Although the tumor from which this cell line originates is very different from ovarian cancer, and these cells...
mulate. Work done by Hasumi et al. (47) supports the hypothesis that blockade of VEGF (and its closely related family members VEGF-B and placental growth factor) is sufficient not only to block ascites formation but also to inhibit the growth of i.p. seeded tumors. They showed that inoculation of RMG-1 human ovarian cancer cells stably expressing the soluble Flt-1 VEGFR results in lower ascites volume and decreased number of cancer cells and number of leaked blood cells compared with animals injected with control tumor cells alone.

Recently, the VEGF-Trap, a high-affinity, soluble decoy receptor capable of blocking both mouse and human VEGF, was described (34, 35). Because the VEGF-Trap is very potent and can block both mouse and human VEGF, we evaluated its effects in mouse models of ovarian cancer. We chose to examine its efficacy in two distinct models of human ovarian cancer. First, we evaluated its effects in the SKOV-3 model. Previously, we showed that VEGF blockade with antibodies prevents ascites formation in a SKOV-3 model (28), and, using the VEGF-Trap, we again demonstrated an effective blockade of ascites formation. Subsequently, we chose to use the OVCAR-3 model, which closely resembles stage 3 human ovarian cancer and is more suitable for evaluating tumor burden as well as ascites. OVCAR-3 tumors express VEGF, carcinomatosis is confined primarily to the peritoneal cavity, and animals develop measurable volumes of hemorrhagic ascites. Within 1 week of initiation of VEGF-Trap treatment, there was a significant decrease in abdominal circumference (reflecting decreased ascites formation) and weight (reflecting decreased tumor burden and ascites) relative to controls. This difference was maintained throughout the experimental period. No visible side effects were evident with treatment. At the time of sacrifice, none of the VEGF-Trap-treated animals displayed ascites or were premorbid, and tumor burden was reduced by ~56% relative to control.

Our study of vascular morphology in the OVCAR-3 model demonstrated that blocking VEGF inhibits leakage, which in turn inhibits ascites formation. Moreover, tumor angiogenesis was also inhibited, and the vessels within the tumors of mice growing in an ectopic site, very similar changes in vascular remodeling were observed (Fig. 6, C and D).

DISCUSSION

The effects of VEGF during the development of human ovarian carcinoma have been studied by several investigators (8, 23, 24, 27, 28, 30, 39, 40). These and other studies indicate that VEGF/vascular permeability factor plays a pivotal role during malignant ascites formation by increasing vascular permeability (7, 23, 41, 42), as well as tumor growth and metastasis.

Whereas other inflammatory factors such as prostaglandins, bradykinin (43), the leukokinin (43), and histamine and other cytokines (43–46) also are thought to be involved in the increased permeability associated with the vasculature in ovarian cancer, various means of VEGF blockade have demonstrated very dramatic inhibitory effects on ascites formation (9, 28–31). Thus, there is strong evidence that VEGF is a causative factor in the formation of ascites in at least some instances. Here we show not only that increased tumor expression of VEGF, using recently developed retroviral vectors, greatly accelerates the onset and amount of ascites but also that overexpression of VEGF alone in the peritoneum using adenoviral vectors, even in the absence of tumor, is adequate to cause ascites formation.

Although VEGF blockade has previously been shown to inhibit ascites formation in several mouse models of human ovarian cancer and has also been shown to inhibit the growth of other solid tumors, its effects on tumor burden in ovarian cancer models have been variable. In part, this is because some models are not well suited to evaluating tumor burden. In addition, the variable results of these studies may be a consequence of the specific characteristics of the reagents used. For example, antibodies to human VEGF are often ineffective in blocking mVEGF. Perhaps the VEGF made by host tissues to which the tumor cells have adhered or invaded is adequate to support tumor vascularization but inadequate to cause ascites to accumulate. Work done by Hasumi et al. (47)

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treated with VEGF-Trap were morphologically distinct from those in control tumors. We questioned whether the dramatic vascular remodeling that occurred as a consequence of VEGF blockade was specific to i.p. ovarian cancer or a general consequence of VEGF blockade. To address this question, we examined the effects of VEGF blockade on the vasculature of a tumor of different origin that was implanted s.c. Strikingly, the vascular morphology adopted by the vasculature of ovarian cancer in the presence of VEGF blockade is very similar to that observed in the vasculature of s.c. implanted C6 glioma tumors in mice that were similarly treated with VEGF-Trap. This suggests that VEGF may be a permissive factor in the development of vascular morphology irrespective of the tumor type or location. Although there are believed to be a number of factors that can promote angiogenesis, we have found that blocking just one of these, VEGF, results in dramatic vascular remodeling, blockade of ascites formation and reduction of tumor burden.

Currently, we are investigating the effects of combining VEGF-Trap treatment with a chemotherapeutic agent, as we have with a VEGF human monoclonal antibody (48). We anticipate that by combining therapies, we will be able to further reduce tumor burden and will prolong response and survival.

Ovarian cancer is a devastating disease for which new treatments are needed. A number of studies suggest that blocking the pathways activated by VEGF will have therapeutic benefit in this disease. Here we show that a novel VEGF blocker has profound effects not only in inhibiting the formation of ascites but also in decreasing tumor burden and remodeling the vasculature.

ACKNOWLEDGMENTS

We are grateful to Joe Pantginis and Patricia Burfeind for technical assistance and to Vicki Lan for graphics assistance.

REFERENCES


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