Differential Involvement of the Hyaluronan (HA) Receptors CD44 and Receptor for HA-mediated Motility in Endothelial Cell Function and Angiogenesis*

Hyaluronan (HA), an important glycosaminoglycan constituent of the extracellular matrix, has been implicated in angiogenesis. It appears to exert its biological effects through binding interactions with at least two cell surface receptors: CD44 and receptor for HA-mediated motility (RHAMM). Recent in vitro studies have suggested potential roles for these two molecules in various aspects of endothelial function. However, the relative contribution of each receptor to endothelial functions critical to angiogenesis and their roles in vivo have not been established. We therefore investigated the endothelial expression of these proteins and determined the effects of antibodies against RHAMM and CD44 on endothelial cell (EC) function and in vivo angiogenesis. Both receptors were detected on vascular endothelium in situ, and on the surface of cultured EC. Further studies with active blocking antibodies revealed that anti-CD44 but not anti-RHAMM antibody inhibited EC adhesion to HA and EC proliferation, whereas anti-RHAMM but not anti-CD44 antibody blocked EC migration through the basement membrane substrate, Matrigel. Although antibodies against both receptor inhibited in vitro endothelial tube formation, only the anti-RHAMM antibody blocked basic fibroblast growth factor-induced neovascularization in mice. These data suggest that RHAMM and CD44, through interactions with their ligands, are both important to processes required for the formation of new blood vessels.

Angiogenesis, the formation of new blood vessels from a preexisting vasculature, is an essential feature of a number of important physiological processes (e.g. wound healing) and pathological conditions (e.g. diabetic eye disease and tumor growth and spread) (1, 2). During this process endothelial cells (EC) in an established vessel initially sever their normal associations with adjacent endothelial cells, migrate, and proliferate into the surrounding tissue, where they reestablish their cell-to-cell attachments to form new capillaries. Given this understanding, the interactions of endothelial cells with the extracellular matrix, and the receptors that mediate these interactions, are of critical importance to the formation of new blood vessels.

Hyaluronan (HA), an important constituent of the extracellular matrix, is a glycosaminoglycan composed of repeating disaccharide units of α-glucuronic acid and N-acetyl-d-glucosamine (3). This ubiquitously distributed molecule regulates cellular events such as cell proliferation and locomotion that are required for a variety of biological processes including tumorigenesis, morphogenesis, inflammation and host response to injury (reviewed in Ref. 4). HA has also been implicated in the formation of vessels. However, its effects in vivo angiogenesis and EC function are complex and have been reported to depend on HA concentration and molecular size (5). High molecular weight HA (at concentrations > 100 μg/ml) inhibits EC proliferation and disrupts confluent endothelial monolayers (6). Consistent with these findings are the observations in chick embryo limb buds that avascular regions are rich in native high molecular weight HA and that expression of this form of HA in normally vascular areas results in decreased vascularity (7). In contrast, low molecular weight HA stimulates EC proliferation (6), induces in vitro endothelial tube formation (8), and stimulates neovascularization in chick chorioallantoic membranes (9) and cutaneous wounds (10, 11).

HA appears to exert its biological effects through binding interactions with specific cell-associated receptors (12). A number of HA-binding proteins have been identified, and two molecularly distinct cell-surface receptors for HA have been characterized, namely CD44 and RHAMM (for receptor for hyaluronan-mediated motility) (12–15). Although several other binding interactions for CD44 and RHAMM have been reported (14, 16), currently the interaction with HA appears to be the one most likely to directly activate intracellular signals required to stimulate processes relevant to angiogenesis. Specifically, preliminary in vitro studies have suggested potential roles for these two molecules in aspects of HA-dependent endothelial function (17–19). However, the relative contributions of each receptor to endothelial functions critical to angiogenesis and their roles in vivo have not been established.

In this paper, we therefore investigated the contribution of the HA-binding receptors, RHAMM and CD44, to EC functions...
and to angiogenesis in vivo. Both receptors were noted to be present on vascular endothelium in situ and on the surface of cultured EC. Using blocking antibodies specific to each receptor, we show that CD44 is the major determinant of EC adhesion to HA and EC proliferation, whereas RHAMM regulates EC migration through the basement membrane substrate Matrigel. Further, although antibodies against each receptor inhibited in vitro endothelial tube formation, only the anti-RHAMM antibody blocked bFGF-induced neovascularization in mice. Together, these data provide evidence for the involvement endothelial HA-binding receptors in specific endothelial cell functions and angiogenesis and suggest that they may represent new targets for anti-angiogenic therapy.

**EXPERIMENTAL PROCEDURES**

**Cell Lines**—Human endothelial cells (HUVEC) and a murine endothelial cell line (H5V), were cultured as described previously (20).

**Reagents and Chemicals**—All reagents and chemicals were obtained from Sigma unless otherwise specified.

**Antibodies**—The following antibodies were used: antibody R36, a rabbit polyclonal anti-serum raised against amino acids 558–605 encoded in the complete murine RHAMM cDNA derived from the RHAMM mouse cDNA library (21), which binds both recombinant smooth muscle cells (22) and murine microvascular endothelial cells on vascular endothelium represent new targets for anti-angiogenic therapy.

**Preparation of Nuclear Fractions of HUVEC Cell Lysates**

- Cells were washed in phosphate-buffered saline (PBS), fixed with 3% paraformaldehyde for 10 min, and then permeabilized with ice-cold 0.5% Nonidet P-40 for 1 min. After washing, cells were stained by immunofluorescent staining using the appropriate antibody as described previously (26).
- Cells were viewed on a Zeiss phase-epifluorescent microscope using a 80× fluorescence lens and photographed with TMAX film at 3200 ASA. Confocal microscopic images were obtained using a computer-interfaced, laser-scanning microscope (Leica TCS 4D) in the Confocal Core Facility at the Children’s Hospital of Philadelphia. Simultaneous wavelength scanning allowed superimposition of fluorescent labeling with fluorescein isothiocyanate and Texas Red fluorophores at wavelengths of 488 nm and 568 nm, respectively. Laser power was fixed at 75% for all image acquisition. Image output was at 1024×1024 pixels.

**Fixed Cell-Dependent Cell Sorting (FACS) Analysis**—Endothelial cells were treated with various anti-human or anti-murine PECAM-1 mAbs for 1 h at 4 °C. The primary antibody was then removed, the cells washed with PBS, and a 1:200 dilution of fluorescein isothiocyanate-labeled goat anti-mouse or anti-rat secondary antibody (Cappell) was added for 30 min at 4 °C. After washing in PBS, flow cytometry was performed using an Ortho Cytofluorograph 50H cell sorter equipped with a 2150 data handling system (Ortho Instruments, Westwood, MA).

**Preparation of Membrane Fractions of HUVEC Cell Lysates**—HUVEC were cultured for 24 h in 96-well plates and the number of viable cells determined using a commercially available non-radioactive colorimetric assay according to the manufacturer’s instructions (Cell Titer 96® AQ®ONE, non-radioactive cell proliferation assay, Promega, Madison WI).

**Adhesion Assay**—HA (as Healon) at a concentration of 0.2 mg/ml in water containing N-hydroxysulfosuccinimide at 0.184 mg/ml, was mixed with an equal volume of 1-ethyl-3-(dimethyaminopropyl)carbodiimide HCl (1.23 mg/ml). 100 μl of the resulting solution was then added to each well of a 96-well plate for 2 h at room temperature, followed by washing of the wells with PBS. In other experiments 100 μl of Matrigel (25 μg/ml; Collaborative Research, Bedford, MA) was added to the well and allowed to dry overnight at 37 °C. The wells with HA or Matrigel coupled to the plate were then blocked with 2% BSA and washed with PBS. EC (20,000 cells) labeled overnight with [3H]thymidine and resuspended in serum-free media containing BSA or antibody were added to the wells and incubated for 30 min at 37 °C in 5% CO2.

**In Vitro Invasion/Migration Assay**—Matrigel-coated transwell inserts (Costar; 8-mm pore filter) were prepared by adding 100 μl of Matrigel (250 μg/ml) to the transwell and allowing the Matrigel to dry at 37 °C in a non-humidified oven for 24 h. EC (100,000 cells) labeled overnight with [3H]thymidine and resuspended in serum-free media containing BSA or antibody were added to the transwells and incubated for 8 h at 37 °C in 5% CO2. The EC pass through the pores of the filter and adhere on the lower surface of the filter (27). After incubation with BSA or antibody, the cells were removed and washed, and the top surface of the filter wiped with a cotton swab. The filters were then carefully cut out, placed in scintillation fluid, and counted in a β-counter. For each antibody condition, migration was expressed as percentage of BSA control.

**In Vitro Tube Formation Assay**—In vitro tube formation was studied using previously described procedures (28). Matrigel was diluted with cold serum-free medium to 10 μg/ml. 50 μl of the solution were added to each well of a 96-well plate and allowed to form a gel at 37 °C for 30 min. HUVEC (150.00 cells/ml) were then incubated for 15 min with IgG or antibody in complete medium. Two hundred μl of the cell/antibody suspension (30,000 cells) were then subsequently added to each well and incubated for 6–8 h at 37 °C in 5% CO2. Under these conditions EC form delicate networks of tubes that are detectable within 2–3 h and are fully developed after 8–12 h. After incubation with IgG or antibody, the tubes were washed and the Matrigel and its endothelial tubes were fixed with 0.5% glutaraldehyde. The tube network was determined by computer-assisted image analysis with the Image-Pro Plus program (Media Cybernetics, Silver Spring, MD).

**Matrigel Model of Cytokine-induced Murine Angiogenesis**—This model has been extensively characterized by Passaniti et al. (29). Briefly C57Bl/6 mice were injected subcutaneously with 0.5 ml of Matrigel supplemented with bFGF (500 ng/ml) to induce the growth of
were found (one-way analysis of variance. When statistically significant differences

were also noted to bind to the vascular endothelium as identified by PECAM-1 (Fig. 1, A–F). Surface expression of RHAMM and CD44 on cultured HUVEC was subsequently demonstrated with these antibodies by confocal immunofluorescence microscopy (Fig. 1, G–I) and by FACS analysis (Fig. 2A). The presence of RHAMM on the cell surface of HUVEC was further confirmed by immunoblotting with anti-RHAMM antibody that demonstrated the presence of RHAMM (~80 kDa) in membrane, cytoplasmic, and nuclear fractions of HUVEC cell lysates (Fig. 2B). Further, the binding of biotinylated HA to HUVEC was inhibited by the either anti-CD44 or anti-RHAMM antibody (Fig. 2C).

Antibody against CD44 but Not RHAMM Inhibited EC Adhesion to HA—A number of important aspects of EC function relevant to angiogenesis including cell proliferation, migration, and tube formation are regulated in part by endothelial adhesive interactions with the ECM (30–32). We therefore investigated the effect of anti-RHAMM and anti-CD44 antibodies on the adhesion of cultured EC to plastic surfaces coated with HA. Although both antibodies inhibited the binding of biotinylated HA to EC in solution (Fig. 2C), antibody against CD44 (20 μg/ml), but not RHAMM (300 μg/ml), inhibited EC adhesion to HA immobilized on plastic (Fig. 3A). This suggests that EC adhesion to HA is largely mediated by CD44, and not RHAMM.

Antibody against CD44 but Not RHAMM Inhibited EC Proliferation—Antibody against CD44 (J-173) has been shown previously to inhibit EC proliferation (17, 18). To determine if antagonism of RHAMM also had a similar effect, HUVEC were cultured for 24 h in the presence of control (anti-MHC1), anti-CD44 (J-173), or anti-RHAMM (R36) antibodies (all antibody concentrations = 100 μg/ml). Compared with cells cultured in media alone, J-173 but not R36 significantly inhibited EC proliferation (Fig. 3C), suggesting that engagement of CD44, but not RHAMM, transduces signals that trigger the proliferation of these cells.

Antibody against RHAMM but Not CD44 Inhibited EC Migration—HA has been implicated in cell motility, including endothelial cell migration (17). We investigated the effect of anti-RHAMM antibody on the ability of single endothelial cells to migrate through polycarbonate filters coated with Matrigel. Antibody against RHAMM, but not CD44, inhibited migration through Matrigel-coated filters in a dose-dependent manner (data shown for 100 μg/ml antibody concentration) (Fig. 3B).

This inhibition is unlikely to be due to antagonism of cell-matrix adhesion, as neither antibody decreased the adhesion of EC to Matrigel-coated surfaces (Fig. 3A), indicating that there are other constituents of Matrigel that allow for EC adhesion to this substrate independent of HA. These data are consistent with a role for RHAMM in the migration of EC through the matrix of the basement membrane.

Antibodies against RHAMM and CD44 Inhibited EC Tube Formation—The differentiation and organization of EC into vascular tubes is a critical step in the process of angiogenesis, which has been reproduced in vitro by a number of models (33). Using a model of endothelial tube formation on Matrigel, we noted that both anti-RHAMM and anti-CD44 antibodies inhibited tube formation by HUVEC on this substrate in a dose-dependent manner (Fig. 4, A and B). Tube formation in the presence of control antibody (anti-MHC1) did not inhibit tube formation (data not shown). Of note, when tube formation was allowed to occur in the presence of both antibodies at concen-
FIG. 2. Expression of HA-binding receptors on EC and their binding of biotinylated HA. A, the expression of PECAM-1, RHAMM, and CD44 on HUVEC and H5V was assessed by FACS analysis. The following antibodies were used: anti-human PECAM-1 (4G6), anti-murine PECAM-1 (390), anti-human CD44 (J-173), anti-murine CD44 (KM81), and anti-RHAMM (R36). Filled and unfilled tracings represent the background staining and staining for the antibodies, respectively. The HUVEC and H5V lines were recognized by the species-specific PECAM-1 antibodies (a and d). Antibody J-173 bound to HUVEC (b), whereas KM81 bound to the H5V line (e). R36 bound to both cell lines (c and f). B, endothelial cell lysates were partitioned into nuclear (N), cytoplasmic (C), and membrane (M) fractions and then blotted with anti-RHAMM antibody. RHAMM (∼80 kDa) was detected in all three fractions. C, the binding in solution of biotinylated HA to HUVEC in the absence or presence of anti-RHAMM or anti-CD44 antibody was determined by FACS analysis. The binding of biotinylated HA to HUVEC, as assessed by the mean fluorescence intensity, was reduced by both antibodies. Data are representative of two experiments in which similar results were obtained.
trations that were individually not inhibitory (anti-CD44 = 5 μg/ml; anti-RHAMM = 50 μg/ml), the inhibition of tube formation was additive (Fig. 4C), suggesting that, with respect to this process, RHAMM and CD44 may act in a cooperative or synergistic fashion.

Inhibition of bFGF-induced Murine Angiogenesis by Anti-
RHAMM Antibody—The finding that various aspects of EC function required for angiogenesis were inhibited by antagonism of RHAMM or CD44 activity suggested that these two HA binding receptors might also be involved in the formation of vessels in vivo. To investigate this hypothesis, we studied the effect of anti-RHAMM (R36) and anti-murine CD44 (KM81) antibodies in a model of murine angiogenesis in which vessels form over 5 days within subcutaneously implanted Matrigel plugs containing bFGF. Non-immune IgG or antibody was incorporated in the plug and administered daily (days 0–4) via the intraperitoneal route (see “Experimental Procedures” for details on dosing). Both antibodies bound murine EC as determined by FACS analysis (Fig. 2A), and KM81 has been shown previously to be a functionally active CD44 blocking antibody (24, 25). Compared with animals treated with KM81 or control animals treated with non-immune rabbit IgG, R36 inhibited the angiogenic response to bFGF (Fig. 5, A–D). As assessed by the hemoglobin concentration in the recovered Matrigel plugs, R36 significantly reduced the vascularization of the plugs whereas the effect of the KM81 was similar to non-immune IgG (Fig. 5E).

**DISCUSSION**

To investigate the involvement of the HA receptors, RHAMM and CD44, in blood vessel formation, the endothelial expression of these proteins was determined and the effects of antibodies against RHAMM and CD44 on EC function and in vivo angiogenesis were studied. Both receptors were detected on vascular endothelium in situ, and on the surface of cultured EC. Further studies with active blocking antibodies revealed that anti-CD44, but not anti-RHAMM, inhibited EC adhesion to HA and EC proliferation, whereas anti-RHAMM but not CD44 antibody blocked EC migration through filters coated with the basement membrane substrate, Matrigel. Although antibodies against either receptor inhibited in vitro endothelial tube formation, only the anti-RHAMM antibody blocked bFGF-induced neovascularization in mice. These data (summarized in Fig. 6) suggest that RHAMM and CD44, through interactions with HA and possibly other ligands, are both important to processes required for the formation of new blood vessels.

EC interactions with the extracellular matrix are integral to the processes required for neovascularization (30–32). A constituent of the ECM that appears to be involved in these events is the glycosaminoglycan, hyaluronan (5), the effects of which are mediated by interactions with at least two cell surface receptors, RHAMM (13) and CD44 (14, 16). Our demonstration of RHAMM and CD44 expression on cultured endothelial cells and on the endothelium of the dermal vasculature supports what others have previously reported (17–19) and is consistent with a putative role for HA in the formation of new vessels. Although we found that biotinylated HA bound to HUVEC, Lokeshwar et al. (19) reported that HUVEC expressed less RHAMM compared with EC from other sources and did not bind [3H]HA. The reasons for these differences are uncertain, but may be related to the sources of the HUVEC, passage number, and/or their state of confluence.

Our report of endothelial surface expression of RHAMM is in agreement with a number of previous reports, which have demonstrated the surface expression of this protein on a variety of non-malignant cell types including smooth muscle cells (22, 34), neuronal cells (35), and thymocyte lymphocytes (36, 37) and fibroblasts (38). Recently, however, the characterization of RHAMM as a surface molecule has been challenged by Hoffman and associates (39). They have proposed, based largely on studies of tumor lines (40–42), that RHAMM is exclusively an intracellular protein, which functions as a cytoskeletal accessory protein and not as a surface receptor for
HA. We would also note that, although there was clearly EC RHAMM that was intracellular (see Fig. 2B), by several approaches we also demonstrated that this protein was present on the surface of endothelial cells (Figs. 1 and 2). The reasons for the differences between our findings and those of Hofmann and colleagues are not entirely clear, but may be related in part to differences in the culture conditions, cell types, and antibodies employed.

The finding of this study that anti-CD44 antibody significantly inhibited the adhesion of HUVEC to immobilized HA (Fig. 3A) confirms the results of investigations with bovine aortic endothelial cells (18). These data are in agreement with previous work, which, for a number of other cell types, has established that their adhesion to HA is mediated by CD44 (14). However, the adhesion mediated by the binding of CD44 to HA is relatively weak in comparison to other cell adhesion mechanisms, such as those involving the integrins (15). This has led to the suggestion that CD44 does not have a primary role in promoting attachments that strongly anchor cells to the matrix. Instead, it may facilitate transient associations that allow for the activation of intracellular cascades involved in processes required for cell activities such cell proliferation or migration (42). In contrast to the anti-CD44 antibody, anti-RHAMM antibody did not block the binding of HUVEC to HA-coated surfaces, although it did inhibit the binding of biotinylated-HA to endothelial cells in suspension (Fig. 2C). This suggests that, unlike CD44, RHAMM functions exclusively as a signaling receptor in endothelial cells.

It has been shown that high molecular weight HA, as well as HA fragments consisting of 10–15 disaccharide units, promote EC proliferation (17–19), including that of HUVEC (17) that is inhibited by anti-CD44 antibody. Consistent with these studies was our finding that antibody against CD44 inhibited the proliferative response under these conditions (Fig. 3C). For cells such as EC, attachment and subsequent spreading appear to be essential for a proliferative response. Thus, the finding that anti-CD44 antibody inhibits EC proliferation, whereas anti-RHAMM antibody does not, is consistent with the presumed role of CD44 in EC adhesion. Further, these data are in agreement with studies of melanoma and hematopoietic progenitor cells, which have shown for these cell types that CD44, but not RHAMM, appears to mediate HA-dependent adhesion and proliferation (44, 45).

Both RHAMM and CD44 have been implicated in cell motil-
ity. For CD44, melanoma cells expressing high levels of specific variants of CD44 display enhanced motility on HA-coated surfaces compared with clones with low or absent expression of the molecule (46–49). Further, recent studies of mouse mammary epithelial cells demonstrate that HA application promotes lamellipodial protrusions in the direction of the stimulus, a process that is inhibited by pretreatment with anti-CD44 antibodies (43). With respect to RHAMM, detailed studies have demonstrated its involvement in the locomotion of transforming growth factor-β-stimulated fibroblasts (50), smooth muscle cells (22), and macrophages (23), as well as that of ras-transformed fibroblasts (38, 51), where RHAMM appears to regulate the turnover of focal adhesions via a protein tyrosine phosphorylation pathway (52).

Although the role of HA receptors in cell migration has been investigated for number of cell types, their role in EC motility has not been extensively evaluated. In the one previous report, the involvement of CD44 in endothelial cell migration was studied by Trochon et al. (17). However, in contrast to the findings reported in this study (Fig. 3B), they observed an inhibition of migration by the J173 antibody. The reasons for these differing results are unclear, but may be due in part to differences in the species and type of endothelial cells investigated (they studied calf pulmonary artery EC and human microvascular EC, whereas we used HUVEC). Another factor may be the migration assays employed by the two groups. Our system was one in which single cells were required to invade and then subsequently migrate through matrix over 6–8 h. Trochon et al. however, used an assay in which cultured confluent endothelial cells on tissue culture plastic were allowed to move over 3 days into a cell-free zone. We would further note that, over 3 days, some of the filling of the cell-free zone will result from the proliferation of EC. As they used an antibody that inhibits EC proliferation and the effects of cell proliferation were not specifically controlled for, some of the inhibition they observed may have been due to inhibition of cell proliferation and not cell migration.

The activity of a specific molecule in the formation of tubelike networks by EC on Matrigel, as inferred by treatments that stimulate or inhibit its expression or function, has been used as model system for predicting that molecule’s participation in angiogenesis in vivo (33). The finding that antibodies against CD44 or RHAMM inhibit tube formation is not unexpected, given the data showing inhibition of EC adhesion and EC migration by anti-CD44 and anti-RHAMM antibodies, respectively. The roles of CD44 and RHAMM in EC tube formation are still remain to be determined. However, the finding that tube formation was partially blocked by the combination of both antibodies at concentrations that were not inhibitory individually suggests that CD44 and RHAMM may act in synergetic way, at least in this Matrigel assay. In light of the above, it is therefore somewhat surprising that, although antagonism of RHAMM or CD44 function inhibited in vitro EC tube formation by HUVEC, only the anti-RHAMM antibody blocked bFGF neovascularization.

We would note that these studies do not necessarily exclude a role for CD44 in vivo angiogenesis. First, although the anti-murine CD44 antibody used in this study has been shown previously to be an effective blocking reagent (24, 25), alternative antibodies may prove to be more effective. Second, the requirement of CD44 for in vivo angiogenesis may depend on the tissue and angiogenic stimulus as has been demonstrated for the αv integrins (32). As this study focused on only one assay, albeit a common one, of in vivo angiogenesis, investigations with other animal models may yield other results. Finally, RHAMM and CD44 may have overlapping or redundant functions as suggested by the studies of tube formation (Fig. 3), and thus RHAMM may be able to compensate for the inhibition of CD44. Studies are now under way with different antibody reagents, CD44 or RHAMM knockout mice, and other model systems of in vivo angiogenesis to address these issues.

Further, it is important to recognize that both RHAMM and CD44 have also been reported to bind to other molecules beside HA. With respect to molecules relevant to angiogenesis, bFGF, fibronectin, and osteopontin have been identified as ligands for different CD44 variants (16, 53–55), whereas heparin has been found to bind to RHAMM (16). Given that the antibody reagents used in this study specifically blocked HA binding, our studies do not rule out the possibility that RHAMM and/or CD44 might also mediate processes involved in angiogenesis through these alternative ligand interactions.

Although our data provide evidence of a role for RHAMM in the formation of vessels in vivo, additional studies are needed to address the issue of overlap or redundancy between these two molecules as well as to determine whether RHAMM or CD44 might be involved in angiogenesis in other systems.

The involvement of RHAMM and CD44 in angiogenesis has been extensively reviewed (16, 53–55). The finding that antibodies against CD44 inhibit angiogenesis in vivo has raised the possibility that the inhibition of angiogenesis noted with our anti-RHAMM antibody in our bFGF model, may also be due to antagonism of RHAMM expressed on relevant non-endothelial cells. Thus, the generation of mutant mice with endothelial-restricted loss of RHAMM should be helpful in specifically confirming the involvement of endothelial RHAMM during in vivo angiogenesis.

In conclusion, these data provide evidence that a number of aspects of endothelial function critical to the formation of new vessels involve the interactions of CD44 and/or RHAMM with their ligands. Further, they suggest that CD44 and/or RHAMM may be potential targets for anti-angiogenic therapy.

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