A great amount of progress has been made in the last few years in elucidating the mechanisms of how blood vessels are formed in both normal and pathological processes. Vasculogenesis and angiogenesis are critical pathways in embryonic development. Aberrant angiogenesis is a major contributor to tumor growth and ocular disease. The discovery of positive and negative regulators of angiogenesis has led to a heightened understanding of how angiogenesis works and to the development of exciting new strategies to inhibit pathological angiogenesis, particularly in cancer. The AACR meeting was organized by Drs. Judah Folkman and Michael Klagsbrun (Children’s Hospital, Harvard Medical School, Boston, MA) for the purpose of updating new developments in angiogenesis research. About 450 people from over 25 countries representing academics, industry, and government attended the meeting, attesting to the heightened interest in the field of angiogenesis. Besides the 25 speakers, over 140 posters were presented.

An important aspect of the conference was the refinement of older concepts of angiogenesis and the presentation of new concepts. Briefly, the topics and new concepts discussed included the following issues.

(a) Normal blood vessel development was discussed. Hemangioblasts are the precursors of endothelial cells. Vasculogenesis, which was previously thought to be restricted to the embryo, occurs in the adult as well by virtue of the recruitment of EPCs from the peripheral circulation. Larger blood vessels are formed by the recruitment of smooth muscle cells, a process regulated by growth factors such as platelet-derived growth factor, transforming growth factor β, and angiopoietins.

(b) Angiogenesis factors and their receptors were discussed. Extensive analysis has implicated VEGF and its two tyrosine kinase receptors, Flt-1 (VEGFR-1) and KDR/Flik-1 (VEGFR-2), as major regulators of normal and pathological angiogenesis. In tumors, VEGF synthesis is regulated by a number of factors including the environment (e.g., hypoxia, glucose levels, and nature of the host tissue), growth factors, oncogenes such as ras, and mutated tumor suppressor genes such as inactivated VHL. Angiopoietins and their receptors, Tie-1 and Tie-2, are also important regulators of angiogenesis. Vascular malformation appears to be a familial syndrome correlated with mutations in and overactivation of the Tie-2 receptor. The intensity of angiogenesis in tumor biopsies has been shown to be diagnostic as a tumor predictor for breast cancers and other tumors. Angiogenesis inhibitors and clinical applications were discussed. Novel strategies for inhibiting angiogenesis and subsequent tumor growth are being developed in many laboratories with potentially exciting therapeutic consequences. One approach has been to antagonize angiogenesis factors such as VEGF and angiopoietin 1 using humanized antibodies and soluble receptors that act as competitive inhibitors. Another approach has been to develop reagents that presumably act directly on endothelial cells to block their migration and/or proliferation or induce endothelial cell apoptosis. These novel inhibitors include angioatin, endostatin, TSP, antibodies directed against the endothelial cell-associated integrin αβ3, ME inhibitors, and IFNs. Mouse models have been established to screen the various antiangiogenesis drugs.

The keynote speaker was N. Le Douarin (Institute of Molecular and Cellular Embryology, Nogent/Marne, France). Dr. Le Douarin discussed the development of blood vessels in the avian embryo, in particular, the concept that there is a hemangioblast that is a common precursor to hematopoietic and endothelial cells. Hemangioblasts express VEGFR-2 (KDR/Flik-1), an endothelial cell marker. Fluorescence-activated cell-sorting analysis was used to isolate VEGFR-2-positive cells from the lateral plate of somites. It was shown that the addition of VEGF caused these cells to become endothelial cells, whereas in the absence of VEGF, the colonies became hematopoietic.

The first session addressed the mechanisms of blood vessel development. P. D’Amore (Children’s Hospital, Harvard Medical School) discussed the regulation of blood vessel assembly in which mural cells (pericytes and smooth muscle cells) are attracted by endothelial cells. In a coculture system, endothelial cells were shown to recruit undifferentiated 10T1/2 mesenchymal cells via the paracrine activity of platelet-derived growth factor BB. Contact between endothelial cells and 10T1/2 cells induced the 10T1/2 cells to express differentiated smooth muscle cell markers including smooth muscle α-actin, smooth muscle myosin, calponin, and SM22. Activated transforming growth factor β was demonstrated to be the inducing agent. Proliferation of both cell types was suppressed in the cocultures, but the identity of the inhibitory activity is unknown. Dr. D’Amore described a differential gene expression study in which quiescent bovine aortic endothelium in vivo expressed a soluble form of FrzA, whereas the expression of soluble FrzA was reduced rapidly when the endothelial cells were cultured. FrzA is a receptor for members of the Wnt family, and soluble FrzA might act as a functional antagonist of Wnt. The role of FrzA and Wnt in vascular growth and differentiation is under investigation.

D. Ingber (Children’s Hospital, Harvard Medical School) discussed the role of mechanical forces and cell geometry in regulating endothelial cell proliferation, differentiation, and apoptosis based on the use of micropatterned substrates. This novel technology uses extra-cellular matrix-coated adhesive islands to vary the degrees of endothelial cell spreading and adhesion and makes it possible to dissociate these two variables and to individually determine their effects on...
endothelial cell function. The bottom line was that cell shape, rather than cell adhesion, governs whether cells proliferate, differentiate, or undergo apoptosis. Cells that are spread grow and have elevated levels of cyclin D1 and decreased levels of the cyclin inhibitor p27. On the other hand, lack of cell spreading leads to apoptosis. Capillary endothelial cells switch into a differentiation program and form hollow tubes at moderate extension with cell-cell contact. In addition, it was pointed out by Dr. Ingber that the architecture of cells depends on a balance of mechanical forces, and that these forces can be transduced into chemical and thermodynamic changes that affect cell function on a molecular level.

There were two presentations describing the novel finding that endothelial stem cells exist in the bone marrow and may play a role in angiogenesis. The conventional wisdom has been that whereas blood vessels in the embryo arise from the development of hemangioblasts into angioblasts (vasculogenesis), postnatal vascularization results exclusively from the proliferation, migration, and remodeling of fully differentiated endothelial cells that are derived from preexisting vessels (angiogenesis). However, it appears that postnatal vasculogenesis can occur and contribute to neovascularization. T. Asahara (St. Elizabeth’s Medical Center, Boston, MA) isolated EPCs from CD34 + hemangioblasts to endothelial cells that differentiated into the endothelial cell lineage in vitro. The EPCs constitute about 0.5–1.0% of the mononuclear cells. Color-tagged EPCs delivered into animals with hind limb ischemia were incorporated into the blood vessels of neovascularizing muscle. The tagged EPCs were also incorporated into tumor blood vessels and the capillaries of animals with myocardial ischemia. Thus, it appears that angiogenesis in the adult is a combination of adult vasculogenesis and sprouting from preexisting vessels.

Along the same lines, S. Rafii (Cornell University Medical College, New York, NY) showed that a small subset of CD34-positive hematopoietic stem cells circulate and differentiate into endothelial cells. KDR (VEGFR-2) is considered to be expressed uniquely by angioblasts and differentiated endothelial cells. Of the CD34-positive stem cells obtained from different sources, about 1–2% were positive for both CD34 and KDR. All CD34/KDR-positive cells had endothelial cell-specific markers including E-selectin and FGF receptor. These cells also expressed a new hematopoietic stem cell marker, AC133. It was shown in a canine model that transplanted bone marrow gave rise to circulating endothelial cells that were incorporated into aortic grafts. Stromal-derived factor 1, a ligand for the CXCR4 receptor on CD34/KDR-positive cells, stimulated the migration of these cells in a modified Boyden chamber assay. It was suggested that upon vascular injury, this chemokine could mobilize bone marrow EPCs to transmigrate into the peripheral circulation, where they could contribute to the acceleration of angiogenesis.

Angiogenesis in brain tumors was discussed by K. Plate (Freiburg University Medical School, Freiburg, Germany). Brain tumors are highly vascular and express elevated levels of VEGF. Glioblastomas expressed higher levels of VEGF as a consequence of hypoxia occurring in tumor cells adjacent to necroses. On the other hand, VEGF production by hemangioblastomas was not hypoxia dependent but was instead up-regulated in stromal cells due to the loss of function of the VHL tumor suppressor gene. The tyrosine kinase VEGFRs Flt-1 (VEGFR-1) and KDR/Flk-1 (VEGFR-2) were not expressed in normal endothelial cells, but they were expressed in tumor vessels. The up-regulation of VEGF expression by brain tumor cells and that of VEGF expression by tumor endothelial cells suggested a paracrine mode of angiogenesis regulation. In addition, an autocrine regulatory mode was suggested in that VEGF up-regulated VEGF expression. Dominant negative VEGFRs inhibited tumor angiogenesis and subsequent tumor growth. These results suggested that VEGF-driven angiogenesis is a key factor in brain tumor development and a potential target for antiangiogenesis therapies as well.

P. Carmeliet (University of Leuven, Leuven, Belgium) used knock-out technology to investigate vascular development and function mediated by VEGF. He and N. Ferrara (Genentech, Inc., South San Francisco, CA) had previously shown that targeted disruption of the VEGF gene leads to embryonic lethality even in the heterozygous state, suggesting that sufficient VEGF levels are needed to mediate angiogenesis in vivo. In collaboration with Dr. P. D’Amore, he used a Cre-Lox approach to generate mice that express only VEGF 120 , the smallest and most readily diffusible of the VEGF isoforms. Fifty percent of the homozygous VEGF 120 mice died within 24 h of birth, and the remainder died within the next 2 weeks. Cardiac myopathy appeared to be a major defect, along with dramatically reduced capillary density and abnormal and fragile blood vessels. Thus, there is a clear need for the larger VEGF isoforms, such as VEGF 164 , for viability. The effects of targeted disruption of the hypoxia-inducible factor element that is responsible for the up-regulation of VEGF expression in response to hypoxia were described. Implantation of targeted ES cells resulted in tumors that were the same size as the wild-type controls but had fewer larger vessels, with the capillary density being equivalent. The tumors in these mice had lower levels of VEGF mRNA, which possibly accounts for the paucity of larger vessels.

The kinetics of angiogenesis in models of tumor progression was discussed by D. Hanahan (University of California San Francisco, San Francisco, CA) as an approach for analyzing the contribution of angiogenesis factors to the vascularization of tumors and screening angiogenesis inhibitors. Three models of tumor progression have been established by expressing dominant oncocenes. They include: (a) islet cell carcinomas that arise as a result of expressing SV40 antigen under the influence of the insulin promoter; (b) bovine papillomavirus type 1-induced dermal fibrosarcoma; and (c) human papillomavirus-induced squamous carcinoma. In the islet model, 100% of the islets expressed SV40, 50% showed prevascular hyperplasia, 10% were angiogenic, and only 2% formed solid tumors. Thus, it appears that at some point, there is a selective switch to an angiogenic state. VEGF and VEGFRs were expressed throughout tumor progression so that the switch to the angiogenic state in the islet system could not be correlated with VEGF expression. However, VEGF levels were up-regulated with progression of the human papillomavirus-induced tumor. The tumor progression models were also useful for testing angiogenesis inhibitors such as the BB-94 inhibitor of MEs and AGM 1470. It was found that these two inhibitors did not affect vascularization as much as increasing tumor cell apoptosis.

New developments in VEGF and VEGFR biology and in potential clinical applications were presented in the next session. K. Alitalo (University of Helsinki, Helsinki, Finland) discussed newer members of the VEGF family, in particular, VEGF-C, which has a role in the lymphatic endothelial system. VEGF-C is made as a precursor protein with a COOH-terminal region rich in cysteine residues. Unlike VEGF, VEGF-C binds and activates the tyrosine kinase receptor Flt-4 (VEGFR-3). Flt-4 is expressed by lymphatic vessel endothelial cells found in normal tissue and tumors such as lymphoma and in situ breast carcinoma, but not by vascular endothelial cells. VEGF-C is an agonist for lymphatic endothelial cells, whereas VEGF is an agonist for vascular endothelial cells. VEGF-C induced a selective growth of lymphatic vessels in 13-day-old chick chorioallantoic membrane. Transgenic mice expressing VEGF-C under a basal epidermal keratin promoter developed a hyperplastic lymphatic vessel network in the skin. Flt-4 knockout mice were embryonic lethal with abnormalities in the yolk sac. VEGF-C, which also binds to KDR/Flk-1 (VEGFR-2), is a much weaker angiogenesis factor than VEGF but has greater VPF
activity than VEGF. A VEGF-C point mutant was found that activated Flt-4 but not KDR/Flk-1. VEGF-B and VEGF-D are other new members of the VEGF family, but they are not yet well characterized. VEGF-B is coexpressed with VEGF and VEGF-C in the heart and muscle and is a ligand for Flt-1. Another family of angiogenesis mediators, the Tie tyrosine kinase receptors, and their ligands, the angiopoietins, were also described. Targeted gene knockout studies indicated that Tie was required during embryonic development for the sprouting of vessels. From these studies, it appears that several ligand/receptor systems exist to regulate different aspects of blood vessel development and function.

Another property of VEGF is its ability to render microvessels hyperpermeable. VEGF is identical to VPF. H. Dvorak (Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA), a discoverer of VPF, discussed the mechanisms of VPF action. VPF introduced into muscle induced both angiogenesis and edema. VPF was proangiogenic by promoting plasma fibrinogen extravasation that clotted to produce a matrix that promoted tumor cell migration and growth and the ingrowth of blood vessels. VVOs are grape-like clusters of interconnected, uncoated vesicles and vacuoles that occupy the EC cytoplasm. VPF increased the permeability of tumor vessels by up-regulating VVO function. When administered in vivo, VPF caused ferritin to leak by extravasation via the VVOs. VVOs may be the major pathway by which soluble macromolecules exit tumor vessels.

There were two reports on the development of VEGF antagonists for use as antitumor drugs. N. Ferrara demonstrated that the majority of human tumors expressed VEGF mRNA, and that VEGF concentrations were elevated in the aqueous and vitreous humors of patients with proliferative retinopathies. Anti-VEGF monoclonal antibodies blocked the growth of human tumors in nude mice. Clinical trials are currently underway to test the efficacy of humanized anti-VEGF antibodies as inhibitors of solid tumor growth. Phase I trials have shown the antibodies to be safe, and Phase II trials are ongoing. In another approach, a portion of the Flt-1 extracellular domain that binds VEGF tightly is being developed as an anti-VEGF reagent. In contrast to the anti-VEGF/tumor studies, it was demonstrated that VEGF in itself has therapeutic uses. For example, recombinant VEGF is in clinical trials for the treatment of coronary ischemia.

K. Thomas (Merck Research Laboratories, West Point, PA) described the existence of a naturally occurring sFlt-1 that may be a natural angiogenesis inhibitor. sFlt-1 is an alternatively spliced variant that results in a truncated Flt-1 protein that contains the NH\textsubscript{2}-terminal six of seven extracellular immunoglobulin-like domains fused to an intron that encodes a 31-amino acid residue COOH-terminal sequence. sFlt-1 is a heparin-binding protein that binds VEGF as avidly as the full-length transmembrane Flt-1. sFlt-1 was synthesized endogenously by vascular endothelial cells and inhibited their mitogenic response to VEGF by sequestering the ligand. It appeared to act in a dominant negative manner by dimerizing with the extracellular domains of full-length membrane-spanning Flt-1 and KDR/Flk-1. HT-1080 tumor cell clones overexpressing sFlt-1 grew much more slowly as s.c. tumors than did control cells. The more sFlt-1 produced, the greater the growth inhibition. Survival was also prolonged in mice injected intracranially with sFlt-1-transfected human glioblastoma tumor cells. Tumor inhibition was attributed to blocking the paracrine effects of tumor-derived VEGF on tumor blood vessels.

In addition to the VEGF family, a relatively new family of angiogenesis mediators, the Tie tyrosine kinase receptors and their angiopoietin ligands, has been investigated recently. According to S. Davis (Regeneron Pharmaceuticals, Tarrytown, NY), Tie receptors are characterized by an immunoglobulin loop, epidermal growth factor-like repeats, cysteine-rich domains, and fibrinogen-like repeats. There are two Tie receptors, Tie-1 and -2, and two ligands, angiopoietin 1 and 2. Gene disruption studies showed that both the Tie receptors and their ligands were necessary for normal angiogenesis to occur. Angiopoietin 1 was not a direct mitogen for endothelial cells, but when it was overexpressed, skin vascularization was increased. In angiopoietin 1 knockouts, no remodeling to produce mature blood vessels occurred. Endothelial cells were round, and there was an absence of pericytes in the vessel. This, it appears that the role of angiopoietin 1 is to recruit pericytes to the endothelium. Whereas angiopoietin 1 is an activator of endothelial cells, angiopoietin 2 is an antagonist. They both bind to Tie-2, but angiopoietin 2 does not induce signal transduction and may be a natural suppressor of Tie receptor function. Moreover, overexpression of angiopoietin 2 destabilized vessels.

B. Olsen (Harvard Medical School) used genetic analysis to make the connection between Tie receptors and vascular malformation, a condition characterized by a relative lack of smooth muscle cells in a blood vessel. In two different families, affected individuals with vascular malformation had a Tie-2 mutation 6 amino acids upstream of an invariant lysine residue, resulting in an Arg to Trp missense alteration. When expressed in cells, the mutant protein was phosphorylated to a 5–10× greater extent than the wild-type protein, suggesting that the mutation resulted in Tie-2 activation. Histological analysis of affected individuals showed dilated vascular channels with a flattened and continuous endothelium. The endothelial cells were firmly attached to the matrix. In contrast to normal blood vessels, which had multiple layers of smooth muscle cells, only patchy and irregular staining of smooth muscle cells was observed. The crystal structure of the angiogenesis inhibitor endostatin was also described by Dr. Olsen. The three-dimensional structure of endostatin was similar to that of E-selectin, an adhesion molecule, although there was only a 9% structure homology.

The role of Tie-2 in pathological angiogenesis was discussed by K. Peters (Duke University Medical Center, Durham, NC), who suggested that inhibiting access to this receptor would inhibit angiogenesis in tumors. A soluble form of Tie-2 consisting of its entire extracellular domain tagged with histidine (ExTek.6His) was developed. ExTek.6His bound with high affinity and inhibited angiopoietin 1-mediated Tie-2 autophosphorylation. The soluble receptor inhibited mammary tumor growth in a rat cutaneous window chamber assay and decreased vascular length density. There was no direct effect on tumor cells in culture, suggesting that the mechanism involved antiangiogenesis. When delivered in an adenovirus vector, the soluble Tie-2 receptor inhibited tumor growth and the development of vascularized lung metastasis. These studies indicate that gene therapy approaches might be of great potential use in inhibiting tumor growth and metastasis.

R. Jain (Massachusetts General Hospital, Harvard Medical School) presented an analysis of the effects of host-tumor interactions on tumor blood vessel properties and VEGF expression. It was stressed that many properties of tumor blood vessels such as angiogenesis, vascular permeability, leukocyte adhesion, and tumor cell VEGF expression levels were varied, depending on the nature of the host tissue. For example, the same colorectal carcinoma cells expressed less VEGF in the liver than in the subcutaneous space. On the other hand, vascular permeability was greater in the liver, probably due to the fenestration of liver vessels. The vascular permeability of a human glioma was much less in the brain than when grown s.c. In general, whereas most tumors are hyperpermeable, each tumor has its own characteristic pore cutoff size and degree of vascular permeability, regardless of VEGF levels. Vascular permeability did not necessarily correlate with angiogenesis, suggesting that VEGF-induced hyperpermeability might not be a prerequisite for angiogenesis, as has been generally considered.

R. Kerbel (Sunnybrook Health Science Center, Toronto, Canada)
suggested that oncogenes might be tumorigenic by inducing angiogenesis. Tumors arise by activation of oncogenes (ras), overexpression of nonmutant proto-oncogenes, (erbB2/neu), and inactivation of tumor suppressor genes (p53 and Rb). In nontumorigenic immortalized intestinal epithelial cells transformed by ras, levels of the angiogenesis stimulator VEGF were increased, whereas levels of the angiogenesis inhibitor TSP were decreased. VEGF up-regulation by ras was necessary but was not sufficient to induce tumor growth in vivo. Another mechanism by which ras transformation resulted in tumorigenicity was the action of the oncogene as a survival factor that prevented apoptosis in tumor cells.

A. Chambers (London Regional Cancer Center, Ontario, Canada) gave a quantitative analysis of how metastatic tumors arise using in vivo videomicroscopy. Most tumor cells survived in the microcirculation and were extravasated from capillaries, but only about 2.5% of these tumor cells formed micrometastases; of these, 1% formed macrometastases with a high proportion of proliferating cells. Thus, many of the extravasated cells survived as single dormant cells in the circulation, whereas only 0.02% of original tumor cells became metastatic tumors. The ME inhibitor BB-94 inhibited the size but not the number of liver metastases. The antimetastatic effects of BB-94 were due primarily to antiangiogenesis rather than effects on extravasation, cell survival, or the formation of micrometastases.

I. Fidler (University of Texas M. D. Anderson Cancer Center, Houston, TX) discussed the importance of the balance of angiogenesis stimulators (e.g., bFGF and VEGF) and inhibitors (e.g., IFNs) in determining whether angiogenesis will occur. In quiescent normal tissues, the inhibitors predominated. Expression studies in human hemangiomas showed that the production of bFGF and VEGF and the absence of IFN-β were associated with the proliferative phase of the tumor, whereas the inverse was true for involuted lesions and normal skin. IFN-α and IFN-β down-regulated bFGF and collagenase expression in many human carcinomas in culture and in vivo. It was clinically determined that continuous, low-dose, long-term exposure to IFN was the most effective mode of antitumor treatment.

In the next session, there were two reports on TSP-1 as an angiogenesis inhibitor. L. Iruela-Arispe (Beth Israel Deaconess Medical Center, Harvard Medical School) described TSP-1 overexpression and targeted TSP-1 knockout experiments. When TSP-1 was overexpressed in the mammary gland, there was a 58% reduction in the vascularization of the tissue. Vascular density was decreased, and capillary loops were more separated. On the other hand, in the absence of TSP-1, there was increased tumor incidence, tumor size, and capillary density. The antiangiogenesis domain in TSP-1 corresponded to the type I repeats. A genetic screen was used to identify other genes with TSP-homologous motifs. Two novel cDNAs were identified that had ME and disintegrin domains typical of the ADAM family in addition to the TSP domain. These were named METH-1 and METH-2. METH-1 and METH-2 suppressed neovascularization in CAM and cornea assays. Expression of these two TSP-1 homologues was relatively low in tumors. These results suggest that a family of TSP-1 angiogenesis inhibitors exists.

N. Bouck (Northwestern University Medical School Cancer Center, Chicago, IL) discussed the regulation of TSP-1 production and activity. TSP-1 production in fibroblasts was dependent on p53. Upon loss of p53, TSP-1 production decreased, and tumor cells became more vascularized. When p53 and ras were coexpressed, TSP-1 expression diminished, and VEGF expression increased. The inhibitory effect of TSP-1 was mediated by interaction with CD36, a transmembrane receptor. CD36 was associated with activated fyn, a src tyrosine kinase. These proteins appeared to be involved in the inhibition of angiogenesis because TSP-1 did not inhibit angiogenesis in mice that failed to make either CD36 or fyn. TSP-1 induced apoptosis in endothelial cells, an effect that could be blocked by anti-CD36 antibodies.

Another strategy for blocking angiogenesis was described by D. Cheshire (The Scripps Research Institute, La Jolla, CA), who showed that angiogenesis depended on cell adhesion via the endothelial cell integrin αvβ3 and proteolytic mechanisms. Antibodies directed against integrin αvβ3 inhibited tumor invasion. An RGD-like peptide, MD 135981, was an αvβ3 antagonist that induced apoptosis and increased p53 and p21 levels. There was no toxicity in Phase I clinical trials, and there were some anecdotal instances of tumor shrinkage. MIs were shown to be involved in regulating αvβ3 activity. Integrin αvβ3 and MMP2 were found to be functionally associated on the surface of blood vessels. The combination of αvβ3 and MMP-2 resulted in the proteolysis of collagen. The COOH-terminal fragment of MMP-2, PEX, was generated autocatalytically, accumulated, and inhibited MMP-2 activity. A mechanism was proposed in which an angiogenesis factor induced the expression of αvβ3, which then bound MMP-2. After matrix collagen was degraded, PEX accumulated and inhibited MMP-2 activity by a feedback mechanism.

The final session of the meeting described the clinical implications of angiogenesis research. W. Linehan (National Cancer Institute, Bethesda, MD) discussed VHL syndrome. There are a number of manifestations of VHL, including hereditary renal carcinoma, CNS hemangioblastoma, retinal angioma, and pheochromocytoma. VHL is a tumor suppressor gene. In patients with VHL, both copies of the VHL gene are inactivated, generally via a mutation in the inherited allele and a loss of the somatic allele. VHL tumors are highly vascular. The renal carcinomas and hemangioblastomas had marked elevations in their expression of VEGF. Reintroduction of wild-type VHL into renal carcinoma cells reversed the phenotype and suppressed VEGF production. VHL tumors are a good example of the strong correlation between tumorigenicity, angiogenesis, and VEGF production.

Angiogenesis can be used as a prognostic marker and a predictor of cancer recurrence. Noel Weidner (University of California San Francisco) showed the results of screening breast carcinoma patients for intratumor microvessel density in biopsies. There was a strong prognostic correlation between microvessel density and tumor aggressiveness. One explanation for these results was that a highly angiogenic primary tumor with a high intratumor microvessel density was more likely to seed distant sites with highly angiogenic clones. The prognostic value of angiogenesis as a marker holds for many other tumors including those of the prostate, but there are exceptions.

The final speaker was J. Folkman, who stated the unifying concept that the microvascular endothelial cells control tumor growth, invasion, metastasis, progression, tumor cell dormancy, and tumor cell apoptosis. It was noted that solid tumors were angiogenesis dependent; surprisingly, leukemias were noted to be angiogenesis dependent as well. The supporting evidence included the presence of high FGF levels in the patients’ urine, the presence of capillaries in bone marrow, and the ability of endostatin to regress leukemias. Endostatin and angiostatin combination therapy resulted in the total regression of tumors. Importantly, this antiangiogenesis therapy was neither toxic nor affected by drug resistance, which are major problems in conventional chemotherapy.

In summary, angiogenesis appears to be a vibrant and rapidly expanding field. The basic goals for the future are to determine in detail the molecular mechanisms that regulate angiogenesis and to determine whether antiangiogenesis therapy has efficacy in the treatment of tumors.
Cancer Research

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