Tumor Angiogenesis:
Feeding the Beast

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The body plastic

During human development, organs and external anatomic structures undergo tremendous growth and remodeling. Throughout this process, mesodermal derivatives such as endothelium and fibroblasts provide essential support for endo- and ectodermal structures which make up our bodies. Surprisingly, throughout adulthood, while we stop visible growth, the plasticity of mesodermal, endodermal, and ectodermal derivatives continues in ways which we still do not fully understand.

The vascular tree in particular displays a remarkable capacity to heal from continual damage, as well as increase or decrease surface area in response to the demands of various tissues. Besides in wound healing, rapid vascularization is seen in the formation of ovarian follicles, with rapid involution of the vasculature following ovulation. Endometrial hypertrophy and sloughing also involves a similar cycle of vascularization and devascularization. Perhaps most revealing is the angiogenesis which accompanies obesity. New adipose tissue, like all tissue, requires sufficient vasculature to avoid necrosis. In the leptin-deficient *ob/ob* mouse obesity model, adipose tissue mass can be dramatically regulated by a variety of angiogenesis inhibitors [1]. In a further refinement of this approach, a peptide homing in on white fat vasculature was recently identified (CKGGRAKDC) using phage display. The peptide, which appears to bind prohibin, was used to reduce adiposity in a non-genetic mouse obesity model [2]. Thus, well into adulthood the vascular tree is capable of extensive regression and redevelopment.

Vasculogenesis and hematopoiesis, brothers in arms

To form tumors larger than ~1 mm^3, cancer cells must pose as normal parenchyma and invoke this vascular plasticity, an event graphically termed flipping the "angiogenic switch." In a number of studies dating from the late 1960's, tumor angiogenesis was found not only to occur in human cancers but to correlate with aggressive characteristics of tumors such as rapid growth, metastasis, and invasion. In animal models as well, such as the Rip1-Tag2 mouse, in which all pancreatic β-cells express the SV40 large T oncogene, neoangiogenesis was found to reliably occur at the transition from hyperplasia to neoplasia [3].

In the same tumor model, conditional knockout of the *vegf-a* gene from the oncogene-carrying cells blocked tumor angiogenesis and abrogated neoplastic tumor growth [4]. In human colon tumors, which also follow a predictable sequence from adenoma to carcinoma, vessel density and expression of a variety of angiogenic substances was found to further increase in the progression from *in situ* mucosal carcinomas to invasive cancers [5]. Thus the angiogenic switch is critical for the appearance of clinically significant cancers. How do tumors appropriate this vascular plasticity and what normal processes do they subvert?

In a surprising pair of studies, investigators studying the Id family of proteins, endogenous antagonists of the extensive basic helix-loop-helix family of transcription factors, found that Id1 and Id3 were heavily expressed in brain endothelium during embryonic sprouting angiogenesis, and were necessary for developmental angiogenesis [6]. Further, since all adult angiogenesis, including tumor angiogenesis, was thought at the time to involve sprouting angiogenesis, Id deficient mice (Id1+/-, Id3-/-) were incapable of invoking tumor angiogenesis. More surprisingly however, the capacity for tumor angiogenesis resided in bone marrow. Thus, transplanting wild-type marrow into Id-deficient mice rescued the tumor angiogenic phenotype, whereas transplanting Id-deficient marrow into wild-type mice suppressed it [7]. Further, using lacZ-transduced cells, the tumor endothelium itself was found to be derived from bone marrow. Thus, a connection between neoendothelium and a compartment associated with hematopoiesis was established.

The intimate relationship between vascular development and hematopoiesis is both ontogenetically and phylogenetically ancient. Ventral mesodermal precursors for both blood cells and blood vessel cells appear simultaneously during human development in the blood islands of yolk sacs. In these structures, hematopoietic and endothelial cells develop in close apposition to each other. Migration of hematopoietic sites occurs, and again hemangioblastic cells reappear in close contact with hemogenic endothelium in the ventral part of the embryonic dorsal aorta. The simultaneous appearance of blood and blood vessel cell precursors in space and time also coincides with strikingly similar gene expressions of the two cell types, with common expression of VEGFR1 and2, CD34, Tie-2, and other markers, suggesting a common precursor, the putative hemangioblast. Developmentally, then, blood cell appearance and development was tied to angioblastic formation of vessels *de novo*, a process called vasculogenesis.

Importantly, the VEGF signaling system, including four known ligands and three receptors, is necessary for the development of both hematopoietic and vascular systems. Thus, absence of VEGFR2 in mice leads to failure of blood island organization, with a lethal absence of both blood and vascular structures [8]. Similarly, even heterozygous deficiency of the *vegf-a* gene leads to catastrophic failure of hemangiogenic structures in mice [9]. The VEGF system even predates the vasculature phylogenetically, as *D. melanogaster*, which lacks endothelium, requires VEGF signaling to establish embryonic hemocyte migrational routes [10]. Mammalian vascular ontogeny therefore may reflect the ventral mesoderm's ultimate capacity to develop both blood cells and their vascular conduits from the same cellular precursors. The VEGF system apparently was coopted to coordinate this development evolutionarily and developmentally.

Conceptually, a connection between the

developmental concepts of hemangiogenesis and the observations that tumor angiogenesis required bone marrow-derived cells came in the finding that endothelial precursors with high proliferative potential could be found in the blood of mature adults [11]. Out of peripheral blood from mouse and human, CD34 positive and negative cells were found to form mixed colonies *in vitro* which functionally resembled yolk sac blood islands. The proliferation and subsequent differentiation of CD34+ cells from spindly stromal cells into morphologically differentiated endothelial cells expressing VEGFR2, vWF, UEA-1, CD31, E-selectin, and LDL receptors required initial contact with CD34- hematopoietic cells. When injected into animals, these cells were incorportated into endothelium *in vivo* [11]. Thus the cellular composition necessary for vasculogenesis is present circulating in the blood of adults, presumably derived from bone marrow. The concept that emerges is that tumors, perhaps by activating the VEGF system, are able to recapitulate developmental vasculogenesis by expanding and mobilizing angiogenic cells from the bone marrow compartment.

Other recent studies have reinforced this scenario of recalling programs previously thought to have disappeared during embryogenesis. Single-cell studies have confirmed the ability of stem cells derived from adult mouse bone marrow to differentiate into all blood lines as well as neoendothelium following vascular injury [12], providing very strong evidence for the existence of adult hemangioblasts. In addition, women receiving male allogeneic bone marrow transplants harbor lung endothelial cells genetically XY, suggesting endothelial chimerism from bone marrow precursors [13]. Similar findings have been reported in the skin and gut of bone marrow recipients, with strong evidence against cell fusion or vertical (fetal) transmission [14]. As expected, VEGF plays an important role in vascular injury models in mobilizing endothelial precursors from the bone marrow, through both direct effects on angioblasts and indirect effects on bone marrow stromal cells to release s-KitL [15]. VEGF also appears to signal upstream of Id1 and Id3, as VEGF fails to mobilize endothelial precursors from Id deficient mice [7].

Besides collaborating within the bone marrow, hematopoietic cells and vasculogenic endothelium may also continue to provide critical paracrine signaling within the tumor neovessels. Bone marrow-derived myelomonocytic cells are frequently seen cuffing tumor neovessels, and selective targeting of such hematopoietic cells causes loss of tumor vasculature experimentally [16]. Perhaps the most striking example of the intimate relationship between tumor neovessels and hematopoitic cells is seen when the cancer

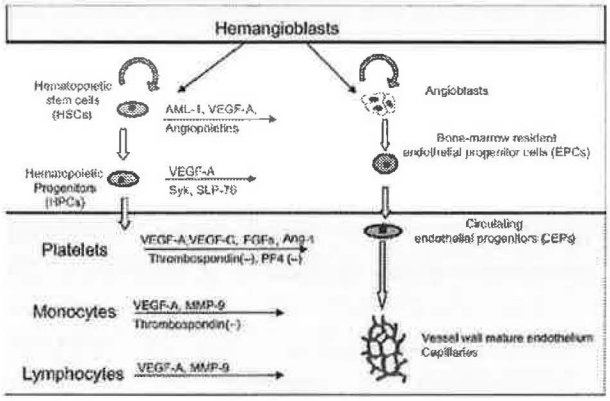

Figure 1 Within the bone marrow niche, stem precursors are stimulated to differentiate forward into both hematopoietic and angioblastic cells, from at least as far back as a bipotent hemangioblast. Committed cells are found circulating in the blood of adults, and paracrine interactions between hematopoietic and endothelial cells continues within the nascent tumor vessels. Diagram from Rafii, Nature Med 2003;9:702.

cell is itself hematopoietic. In a study of 27 B-cell lymphomas, in all cases the tumor endothelium displayed the same chromosomal primary translocations as the lymphoma [17]. Secondary chromosomal abnormalities of individual lymphomas were also invariantly found within tumor endothelium.

Generalizing the angiogenic switch

Extrapolating the codependence of vascular and blood cell development in cancer evolution, one might expect to find that hematopoietic malignancies should display angiogenic switch activation even in the absence of a solid tumor, and this in fact appears to be the case. For such "liquid tumors," angiogenesis appears in the bone marrow itself. In the bone marrow of patients with B-cell NHL, for example, microvascular density is higher than is found in benign forms of lymphadenopathy, and vascularization correlates with lymphoma grade [18]. Bone marrow vascularity is also increased in AML, CML, ALL, P. vera, and MDS, with higher VEGF plasma levels found in many leukemias [19-21]. Bone marrow from multiple myeloma patients also exhibit higher microvascular densities, which again correlates with clinical grades of aggressiveness [19]. Accordingly, bone marrow vascularity correlates with plasma cell proliferation and predicts outcome in plasma myeloma patients [22]. A murine 5T2 myeloma model confirms that an angiogenic switch is activated during the rapid expansion phase of the disease, correlating with a shift to a more primitive plasma cell phenotype [23].

The bone marrow angiogenic activity in hematologic malignancies appears in some ways to be a dysregulation of the normal paracrine signaling which fosters both vasculogenic and hematopoietic cell proliferation. Thus, leukemic, lymphoma, and myeloma cells express and secrete VEGF, and endothelial cells exposed to VEGF express the hematopoietic chemokines IL-6, M-CSF, and GM-CSF [24]. IL-6 is also secreted by bone marrow stroma, which induces myeloma cells to secrete VEGF [25], and myeloma cells are angiogenic in chick allantoic membrane assays [19].

A logical but unanswered question, given the probable importance of paracrine signaling in liquid tumor-associated angiogenesis along with the absence of a tumor proper, is whether angiogenesis is required for blood flow or only for paracrine interaction between cancer cell and endothelium. Bone marrow endothelia in hematologic malignancies is disorganized and often appear in sprouts lacking lumina [21, 26]. Following chemotherapy-induced unpacking of bone marrow of ALL cells, the neoangiogenic lumina are generally dilated and empty [26], suggesting perhaps that the endothelium in fact may not serve a conduit function in its support of hematologic cancer. The same question of the importance of conduit function may be asked of solid tumors, especially since only ~1% of tumor neovessels are thought to be actively perfused with blood at any one time. Again, there is developmental precedent for a paracrine collaboration between endothelial cells and endodermal epithelium, independent of blood flow. In VEGFR2-deficient mice, lacking endothelial cells, hepatic endoderm arrests after budding, whereas normally endothelial cells invade and comingle with the developing liver parenchyma [27]. At this stage, there is no blood flow. The dependence of liver development on endothelium was confirmed in embryonic tissue explant systems, in which again there is no blood flow. Similarly, pancreatic gland formation is arrested in the absence of endothelial cells, long before blood circulation starts [28]. Thus the embryonic endothelium is capable of nurturing

organogenesis independent of blood conduit function, prompting the observation that endothelium is like "chicken soup for the endoderm" [29]. The extrapolation to solid malignancies is unknown, although perivascular cuffing of tumor cells around vessels is seen, especially at the advancing edge of melanomas and prostate cancers [30], again suggesting a paracrine interaction between endothelial and cancer cell. Thus feeding the beast–the dependence of the tumor upon its stroma–may extend beyond supplying blood flow.

The tumor as neoorgan: Recapitulation of mesodermal developmental programs

A parallel can be drawn between normal organogenesis, in which somatic stem cells interact with primitive mesodermal cells to form differentiated parenchyma and vasculature, and tumorigenesis, in which tumor stem cells reactivate a mesodermal program highly reminiscent of developmental vasculogenesis to call forth vascular and blood precursors, forming tumor stroma and vasculature. In this sense, the tumor represents a neoorgan, invoking mesodermal developmental processes albeit in an uncontrolled fashion. To the extent that cancer cells do not allow the endothelium to complete vascular maturation, tumors truly resemble wounds which do not heal.

Importantly, this incomplete maturation implies that the phenotype of tumor endothelium is different from that of normal, quiescent vasculature. Indeed, the tumor vasculature is chaotic, lacks hierarchical branching patterns [31], and has very different expression profiles [32]. Tumor endothelia are hyperproliferative, with ~25% of cells actively incorporating thymidine (compared to ~0.01% of normal endothelium); tumor endothelium displays marked differences in its cytoskeleton which accompanies migration and invasion capabilities; and tumor endothelium possess different adherence and intercellular contact properties which allow them to float freely in the blood stream and grow on top of one another [31, 33]. Thus, tumor endothelium expresses the same phenotype as tumor cells themselves, in their ability to metastasize, invade, and proliferate. In this sense, the significance of the angiogenic switch may be that for a cancer to conquer the body and gain the capacity to form a neoorgan, it must convince innocent stromal cells to march in lock step with it, phenocopying its abnormal cellular behavior.

As may be expected, there is broad overlap between the signal transduction

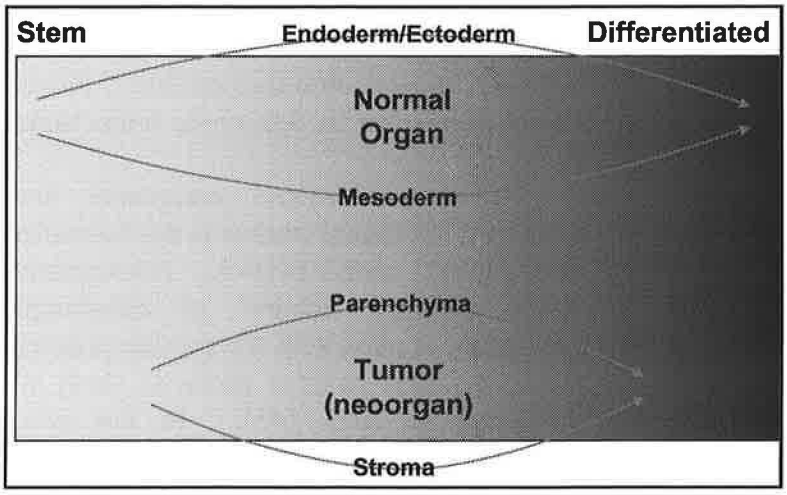

Figure 2 Tumor development in part mimics that of a normal organ. Tumor stroma, especially the vasculature, arises from mesodermal precursors held within the bone marrow. The incomplete maturation of both cancer and endothelial cell provides a rationale for therapeutic targeting.

pathways constitutively activated in tumor cells and those externally activated in angiogenic endothelium. These include integrin and receptor tyrosine kinase-activated pathways involved in Ras and Rho family GTP loading, PI3K/Akt activation, MAPK and mTOR activation, and HIF family activation. Not surprisingly, then, many forms of conventional chemotherapy, which capitalize on the hyperactivation of such pathways in tumor cells, have been found to be antiangiogenic by virtue of their activity on tumor endothelium. Vinblastine at a low, nontoxic dose, for instance, can block experimental angiogenesis [34], and even more highly targeted drugs can diminish angiogenic activity. Anti-Her2/Neu (Herceptin) reduces VEGF and angiopoietin-1 levels and thus diminishes tumor blood vessel diameter and vascular permeability [35], and anti-EGFR (Cetuximab) decreases tumor expression of VEGF and IL-8, thus decreasing microvascular density [36]. Similarly, tumor endothelium is the primary target of lower doses of ionizing radiation in experimental fibrosarcomas or melanomas [37]. In this latter model, endothelial acidic sphingomyelinase appears to be necessary for vascular cell apoptosis from radiation.

A corollary of the concept that the tumor vasculature can be redefined as the primary chemotherapy target is that drug dosing schedules may be revised to account for the fact that the genetically normal endothelium should not become drug resistant. This concept was advanced using cyclophosphamide in murine tumors, using the observation that following a relatively low single dose of drug a transient pulse of tumor endothelial apoptosis preceded tumor cell death [38]. By pulsing drug administration at low, frequent doses, persistent tumor endothelial killing and cure from the experimental tumor was achieved, even in tumors derived from cyclophosphamide-resistant cells. This low, frequent dose schedule, called metronomic treatment, has been extended to more specific antiangiogenic drugs as well [39]. A number of clinical metronomic therapy-based trials are underway presently.

Neoorgan targets: a) VEGF

The striking difference between normal and tumor endothelium also offers a potential therapeutic window to treat tumors by targeting their vascular supply. The angiogenic endothelial cell for the most part responds to abnormal signals with a genetically normal program, and a logical angiogenic signal to pharmacologically target is VEGF. VEGF expression rises abruptly during the transition from colon *in situ* carcinoma to invasive submucosal carcinoma, along with tumor vessel density [5]. In addition, immunohistochemical levels of VEGF and VEGFR2 correlate with metastatic and proliferative behavior of colon cancers, and VEGF tumor levels also predict prognosis in node-negative breast cancer [40, 41]. These clinical observations fit well with the aforementioned role of VEGF in mobilizing neoangiogenic cells from the bone marrow niche during tumor angiogenesis. Experimentally, VEGF induction is necessary for growth of murine Rip-Tag islet neoplastic tumors [4], and VEGF induction by gliomas is necessary to overcome angiopoietin-2-induced vessel regression in orthotopic brain tumors [42].

The anti-VEGF compound most advanced in clinical studies is the humanized monoclonal anti-VEGF-A, bevacizumab. After a large number of encouraging preclinical studies with the murine precursor MAb, the first positive phase II study was published in 2003 [43]. In this study, bevacizumab was used as a single agent

against metastatic clear cell renal carcinoma. The choice of tumor was logical, as most clear cell tumors have lost von Hippel Lindau protein expression, leading to higher HIF-1α levels and consequent VEGF hyperexpression. The study was halted at the second interim evaluation because the primary endpoint, time to tumor progression, was already different. At 10 mg/kg, there was a 2.55-fold increase in time to progression, though no difference in survival was noted. Besides epistaxis and hematuria, hypertension and proteinuria were also noted as possible adverse effects.

A second phase II study targeted NSCCA of the lung, this time on a chemo platform of pacitaxel+carboplatin [44]. There was a significant increase in the primary endpoint, time to progression, with the higher dose, 15 mg/kg, from 4.2 to 7.4 months. In addition, the response rate improved (31.5 vs 18.8%) and the survival increased modestly (17.7 vs 14.9 months). Notably, six patient (five receiving low dose and one receiving high dose bevacizumab) experienced significant hemoptysis, fatal in four. In all cases, the primary tumor was central in location, and in four of six the cell type was squamous. A current phase III study in lung cancer excludes squamous cell carcinoma.

Both positive and negative phase III studies have now been published for bevacizumab. The pivotal study targeted metastatic colon cancer, with the published data performed on a chemo platform of irinotecan, 5-FU, and leucovorin [45]. The primary endpoint, median survival, improved from 15.6 to 20.3 months, and only hypertension was found to occur with a significantly increased frequency. Thus metastatic colon cancer remains the only FDA indication for this compound. A nonreported group used early in the study used FU/LV as the platform, and apparently bevacizumab showed activity here as well, with a median survival of 18.3 months. In a subsequent clinical study, bevacizumab given alone as a pretreatment was studied and found to reduce tumor blood flow and microvascular density, though only one of six tumors regressed in size after 12 days [46].

The second phase III study to be published involved a heavily pretreated group of patients with metastatic breast cancer, having failed anthracycline/taxane class treatment [47]. Using capecitabine as the conventional drug, bevacizumab showed no survival advantage. At least one other phase III study targeting breast cancer with paclitaxel-containing regimens is underway.

Another class of promising compounds are small molecule kinase inhibitors relatively selective for the kinase domain of VEGFRs, especially VEGFR2. The lead compound of this group, PTK-787 (PTK/ZK), which inhibits VEGFR1,2,3, c-Kit, and PDGFR, has had significant antitumor effects demonstrated in a number of preclinical studies, and is presently in phase III trials. A second compound, SU11248, apparently has shown survival efficacy in a phase III study of Gleevec-failed GIST (www.gistsupport.org, 1/05).

Because the efficacy of anti-VEGF therapy when used alone has been relatively modest, especially compared with its effect in combination with traditional chemotherapeutics, a reconsideration of its mechanism of action has been called for. One explanation, for which there is some supportive data, is that anti-VEGF strategies transiently normalize tumor vasculature, thus sealing up leaky vessels and reducing intratumoral interstitial pressures [48]. In this scenario, transiently improved tumor perfusion may increase chemotherapy delivery, and increase tumor oxygen tension for radiation sensitization. Thus a drug "window" 4-5 days after anti-VEGF treatment has been proposed,

during which the effects of conventional cancer treatment may be enhanced [49]. At this point, however, the most efficacious strategy for use of bevacizumab and other anti-VEGF compounds has yet to be determined.

Neoorgan targets: b) integrins

Integrins are heterodimeric transmembrane complexes which connect insoluble matrix outside the cell with the insoluble cytoskeleton inside. In addition, integrins provide context for growth factor signaling and thus impart positional control to receptor tyrosine kinases and permit (or deny) cell survival. Integrins also intimately control actin rearrangements necessary for migration and retraction through activation of Rho family GTPases. At least 24 different integrin combinations are expressed, as each integrin pair displays differential preference for different matrix proteins as well as different internal signaling complexes. Thus integrins are well known to transduce outside-in signals, reporting to the cell the nature of its surroundings, as well as inside-out signals, allowing the cell to dictate its propensity for adhesion and traction. Angiogenic endothelial cells display enormous dynamism in their integrin and related cytoskeletal signaling networks, and accordingly tend to selectively express integrins associated with actin rearrangement, proliferation, and survival (such as $\alpha v\beta 3$, $\alpha 5\beta 1$, and $\alpha 6\beta 4$) rather than the more cytostatic integrins. Not surprisingly, cancer cells themselves also engage in integrin switching, selectively expressing these same integrin pairs. Again, the tumor creates a phenotypic template for its stroma to mimic.

Animal studies have generally supported the importance of certain integrins in vasculogenesis. $\alpha 5$-/- mice, for instance, develop severe mesodermal defects. In particular, yolk sac blood islands do not fuse, and dorsal aortae fail to close [50]. Further, cytosolic truncations of $\alpha 6\beta 4$ integrins decrease tumor angiogenesis in transgenic mice [51]. However, both mice and people lacking $\beta 3$ appear to have platelet disorders but normal vasculature [52, 53]. In fact, mice deficient in $\beta 3$ integrins display enhanced tumor angiogenesis [54], suggesting that $\alpha v\beta 3$ may be antiangiogenic, and antibodies or peptides directed against it may instead act as agonists [55].

Notwithstanding, a number of anti-integrin compounds have been developed. Some of the first compounds to be discovered were endogenous angiogenesis inhibitors such as angiostatin and endostatin, which bind $\alpha v\beta 3$ and $\alpha 5\beta 1$, respectively [56-60]. Interestingly, both of these compounds were found to be proteolytic fragments of non-antiangiogenic matrix proteins (plasminogen and collagen XVIII). Thematically, other antiangiogenic peptides have been since discovered, which again are proteolytically released fragments of matrix proteins (tumstatin from colIV-$\alpha 3$, endorepellin from perlecan) which bind angiogenic integrins in an atypical fashion [61, 62]. Supportive of a physiologic role for these fragments, mice lacking tumstatin or endostatin show increased tumor angiogenesis and increased tumor growth [60, 63], whereas mice overexpressing endostatin have diminished tumor growth. Interestingly, endostatin decreases Id1/3 expression and reduces mobilization of endothelial precursors from the bone marrow [64, 65]. Finally, several compounds have been developed to specifically target angiogenic integrins, such as a monoclonal antibody against $\alpha v\beta 3$, which show activity in animal models [66].

The anti-integrin compounds have not advanced nearly as quickly as the anti-VEGF drugs through clinical testing, perhaps suggesting a lower level of efficacy. At least

two compounds, anti-αvβ3 (Vitaxin) and a cyclic integrin-binding peptide, EMD-121974, are presently in phase II trials.

Neoorgan targets: c) cytoskeletal agents

A third general class of antiangiogenic drugs targets and disrupts the endothelial cell cytoskeleton. While the cytoskeletal proteins, such as actin and tubulin, are no different in the angiogenic endothelium as in any other cell, the cytoskeleton is used both for extensive physical changes (necessary for migration and invasion) as well as internal cell signaling, for which it acts as a dynamic protein scaffold. Two compounds worthy of mention are combretastatin A (or the phosphated prodrug CA4P) and 5,6 dimethylxanthenone-4-acetic acid (DMXAA). CA4P, originally isolated from the Cape Bushwillow tree, is a chemical and functional analog of the tubulin-binding drug colchicine, and has effects on both microtubules and actin microfilaments, leading to cell retraction and membrane blebbing [67, 68]. DMXAA, in contrast, appears to depolymerize actin. Both compounds have remarkably rapid, profound, and often prolonged effects in decreasing tumor perfusion, with subsequent vascular congestion and hemorrhagic necrosis [69, 70]. At tumor ischemia-inducing doses, perfusion to normal organs does not suffer significantly in mouse models [70]. These effects stand in contrast to many if not most of the anti-integrin compounds, which prevent tumor growth but rarely cause tumor regression.

Several compounds from this class are in phase II testing. In a phase I dose-response study, DMXAA was pushed to high levels, causing worrisome ischemic symptoms, though these doses are likely supratherapeutic [71]. CA4P has also undergone phase I dose escalation with thrombocytopenia emerging as the dose-limiting effect [72]. Further clinical data is awaited.

Postscript

The most effective use of antiangiogenic therapy in cancer treatment is unclear at the present time. The published clinical trials may be taken as proof of principle that such an approach will add to conventional therapy. Ultimately, however, at least two valuable lessons may be gleaned from the antiangiogenic movement. First, consideration may be focused on the tumor as an aberrant developing organ, allowing targeting of both cancer and stromal cells, both of which deviate biochemically and functionally from their normal counterparts. Indeed, the cancer cell becomes clinically important only at the point at which it acquires the capacity to appropriate normal developmental programs. Second, as further knowledge is gained about how the cancer cell manages to reactivate such primitive programs, it may become possible to treat degenerative diseases such as emphysema, neurodegeneration, or ischemic vascular disease by turning on these same programs in normal parenchymal cells. Thus, a detailed understanding of the relationship between tumor and tumor stroma may yield treatment for the most common lethal diseases in America, those of neoplasia and those of degeneration.

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