Molecular angiogenesis

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New insights into the mechanisms by which blood vessels develop (angiogenesis) have been gained recently, primarily by the identification of factors that inhibit and promote this process. Angiogenesis-stimulating factors are being used to promote growth of new blood vessels in ischemic disease. In contrast, anti-angiogenesis factors are being used as inhibitors of neovascularization to control tumor growth and metastasis.

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Introduction

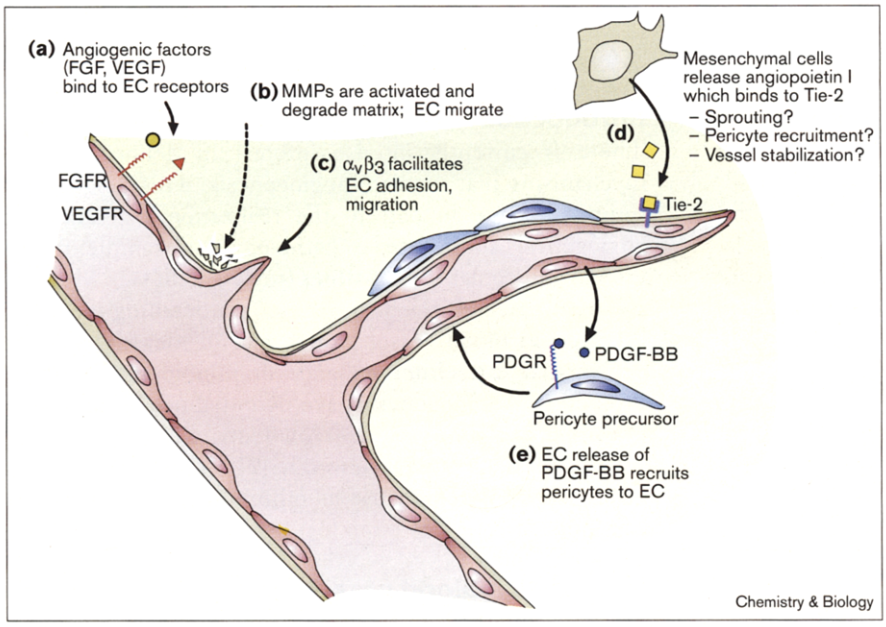
There is currently intense interest in delineating the mechanisms that regulate angiogenesis. This heightened scrutiny is due in part to the realization that aberrant angiogenesis contributes to pathology, for example, tumor growth and ocular retinopathies (reviewed in [1]). Much of the basic research has been focused on detailing the steps involved in blood vessel growth and in identifying molecules that can either enhance or inhibit angiogenesis. Promoters of angiogenesis have potential use in treatment of cardiac and limb ischemia (inadequate blood supply to an organ or body part; reviewed in [2]). Inhibitors of angiogenesis have potential use as inhibitors of tumor growth and metastasis (reviewed in [3]).

How does a blood vessel form?

Blood vessel formation occurs through the processes of vasculogenesis and angiogenesis [4–6]. Vasculogenesis is the differentiation *de novo* of vascular endothelial cells from precursor cells, known as angioblasts, during embryonic development. This process is distinct from angiogenesis, which is a remodeling process characterized by the sprouting of new blood vessels from pre-existing ones. Vasculogenesis was thought to occur only in early embryogenesis. The existence of endothelial progenitor stem cells has been recently established, however, and these bone marrow-derived cells have been found to be incorporated into neovascular foci in the adult, including injured corneas, ischemic hindlimbs and tumor vasculature, suggesting that vasculogenesis can occur in the adult [7–9]. Angiogenesis occurs during embryogenesis and to a limited extent in the adult, for example in the female reproductive system, in physiological wound healing and in pathological disease processes such as cancer.

The individual events that occur during angiogenesis are shown schematically in Figure 1. Angiogenesis is stimulated by factors such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), which will be described at greater length below. An early response to angiogenesis-stimulating factors is the degradation of endothelial cell basement membrane by proteases, for example, by members of the matrix metalloproteinase (MMP) family. MMPs degrade collagen and other extracellular matrix components, disrupting the basement membrane barrier, enabling endothelial cells to migrate from pre-existing vessels towards angiogenic stimuli and to proliferate (reviewed in [10]). Vascular cell-adhesion molecules contribute to endothelial cell migration by mediating cell–extracellular-matrix interactions. An important mediator is the integrin $\alpha_v\beta_3$, a receptor for Arg–Gly–Asp

Figure 1



Processes in angiogenesis – the various steps in blood vessel formation. **(a)** Angiogenesis factors bind to their receptors on endothelial cells (EC) activating signal transduction pathways. **(b)** Matrix metalloproteinases (MMPs) are activated that degrade extracellular matrix allowing endothelial cells to migrate out of the pre-existing capillary wall and to proliferate. **(c)** Integrin $\alpha_v\beta_3$ is expressed by endothelial cells facilitating their adhesion to the extracellular matrix and their migration. **(d)** Angiopoietin-1 (Ang1) binds to Tie-2 receptors on endothelial cells. The result of this interaction is not clear at present but it has been suggested that Ang1 stimulates vessel sprouting, pericyte recruitment, and/or vessel survival and stabilization. **(e)** Endothelial cells release PDGF-BB, which is a chemoattractant for pericyte precursors. These cells become associated with endothelial cells and differentiate into pericytes. Endothelial cells not covered by pericytes regress (not shown).

(RGD)-containing proteins such as fibronectin, which is expressed at low levels in quiescent blood vessels (reviewed in [11]). Integrin $\alpha_v\beta_3$ expression is induced following exposure to angiogenesis-stimulating factors, preferentially on the surface of endothelial cells in newly forming capillaries. Antagonists of $\alpha_v\beta_3$ inhibit the growth of new blood vessels but not pre-existing ones, suggesting that cell adhesion is a critical step in angiogenesis [12]. Following migration and proliferation, endothelial cells assemble into tubes that have a patent lumen. Lumen formation may be dependent on E-selectin, a transmembrane cell-adhesion glycoprotein that mediates endothelial cell–cell contacts [13]. The nascent tubes form a primary vascular network. Following formation of small blood vessels, remodeling occurs to form larger mature vessels. An important step in producing a mature blood vessel is the recruitment of mesenchymal cells and their subsequent differentiation into smooth muscle cell-like pericytes that are thought to stabilize the newly forming vasculature. Pericytes are gradually attracted to a preformed endothelial plexus leading to progressive covering of the vascular tree [14]. During this period, regression of uncovered capillaries occurs, which ceases after acquisition of a pericyte coating. This later phase of blood vessel formation, therefore, is characterized by remodeling steps in which unprotected vessels are pruned and pericyte-covered vessels become stabilized and less prone to destabilization and regression.

Platelet-derived growth factor (PDGF) plays a role in pericyte recruitment [15]. The PDGF-BB isoform is a potent chemoattractant and mitogen for pericytes and smooth muscle cells. PDGFB-deficient mouse embryos are characterized by a lack of pericyte association with blood vessels in some tissues. Furthermore, several microvascular beds are dilated and display microaneurysms with hemorrhaging and edema occurring. These results suggest that PDGF-BB, probably from an endothelial cell source, recruits pericytes to associate with endothelial cells to increase blood vessel stability.

Promoters of angiogenesis

Vascular endothelial growth factor (VEGF) and its receptors

VEGF plays a major role in regulating normal embryonic vasculogenesis and angiogenesis as well as tumor angiogenesis (reviewed in [16–19]). VEGF is a 40–45 kDa homodimeric protein released by a number of cell types including most tumor cells. It is identical to vascular permeability factor (VPF). VEGF monomers exist as five different isoforms of 121, 145, 165, 189 and 206 amino acids that are produced by alternative splicing from a single gene containing eight exons. $VEGF_{121}$ and $VEGF_{165}$ are the most abundant isoforms. Although $VEGF_{121}$ is freely diffusable, $VEGF_{165}$ binds to heparan sulfate and becomes partially associated with cell surface and extracellular matrix heparan sulfate proteoglycan. Recently, other structurally homologous members of the VEGF family have been identified including placental growth factor (PLGF), VEGF-B, VEGF-C, VEGF-D and VEGF-E (reviewed in [19,20]). VEGF activities are mediated by high affinity receptor tyrosine kinases (RTKs) associated primarily with endothelial cells. Two VEGF RTKs have been identified, the 180 kDa fms-like tyrosine kinase (Flt-1) [21] and the 200 kDa human kinase insert domain-containing receptor (KDR) and its murine homolog, Flk-1 [22]. VEGF binds

to both Flt-1 and KDR/Flk-1 with high affinity but the VEGF signal that induces chemotaxis and mitogenicity is transduced preferentially via KDR/Flk-1 [23]. VEGF-C binds to a third structurally related RTK, the 180 kDa Flt4, which is preferentially expressed on lymphatic endothelium [24]. Recently, neuropilin-1, a neuronal cell receptor that mediates neuronal guidance, has been identified as a receptor for VEGF as well [25]. Neuropilin-1 binds $VEGF_{165}$ but not $VEGF_{121}$. Neuropilin-1 differs from the other VEGF receptors in that it does not appear to be a tyrosine kinase receptor. In addition, it is expressed abundantly by nonendothelial cells, for example, tumor cells, thus allowing these cells to bind $VEGF_{165}$ in the absence of Flt-1 or KDR/Flk-1. Interestingly, other neuronal guidance molecules such as the ephrins have been recently reported to be angiogenic [26].

Targeted gene-disruption experiments have provided clues to the function of VEGF and its receptors. In each case, targeted disruption of VEGF of a receptor is embryonic lethal. Targeted disruption of even one allele of the VEGF gene results in impaired blood vessel formation and growth retardation suggesting tight dose-dependent regulation of embryonic vessel development by VEGF [27,28]. Targeted disruption of the KDR/Flk-1 gene in mice results in early defects in the differentiation and development of endothelial cells [29]. In these mice, yolk-sac blood vessels are absent and there are no organized blood vessels at any stage. In targeted disruption of Flt-1, normal endothelial cell differentiation from precursor cells occurs, but endothelial cell assembly into blood vessels is impaired [30]. Therefore, Flk-1 seems to function earlier than Flt-1. In mice targeted for disruption of Flt4, vasculogenesis and angiogenesis occur but large vessels become abnormally organized with defective lumens [31]. These results suggest a role for Flt4 in embryonic vascularization before emergence of the lymphatic system. Targeted disruption of neuropilin-1 results in embryonic death because of cardiovascular defects [32].

Although developmentally significant, VEGF-mediated angiogenesis is rare in the adult. One exception is the female reproductive system where it has been demonstrated that VEGF expression is correlated with vascularization of ovarian follicles, development of the corpus luteum, repair of endometrial vessels and angiogenesis at the site of embryo implantation [33]. VEGF-induced angiogenesis may also be involved in physiological wound healing and tissue repair. Use of VEGF for inducing collateral development in ischemic patients will be described below.

VEGF is a prime contributor to tumor angiogenesis. Most tumor cells produce high levels of VEGF and VEGF receptors are associated with tumor endothelial cells. [18,34,35]. VEGF expression is induced by oncogenes such as *Ras* and inhibited by tumor suppressors such as von Hippel Landau (VHL) protein [36]. Inactivation of VHL results in overproduction of VEGF. VEGF expression is upregulated by hypoxia and is often elevated in regions of tumor necrosis (reviewed in [37]). Hypoxia upregulates VEGF expression by activating a hypoxia-inducible factor-1 (HIF-1)-binding sequence in the VEGF promoter, which results in increased VEGF mRNA transcription and stability. Taken together, these data provide evidence that VEGF is a tumor-derived paracrine angiogenesis factor whose expression results in the delivery of the O_2 and nutrients needed for tumor growth.

Angiopoietins and Tie receptors

Tie receptors and their ligands, the angiopoietins, (reviewed in [38,39]) play a critical role in embryonic angiogenesis, but not vasculogenesis. Tie receptors, Tie1 and Tie2 (also known as Tek), are tyrosine kinases expressed by endothelial cells. Tie expression follows VEGF receptor expression and these receptors support functions of more mature endothelium, for example, vessel sprouting, branching and stabilization of vascular networks [40]. Mice deficient in Tie2 are embryonic lethal with defects in the proper development of the endothelial lining of the heart. The primary capillary plexus fails to remodel into small and large vessels [41,42]. Tie1 is required for the structural integrity of endothelial cells. Mice deficient in Tie1 die by birth due to edema and hemorrhaging [42].

Angiopoietin-1 (Ang1) is a ligand for Tie2 [43]. A ligand for Tie1 has not yet been described. Ang1 (70 kDa) induces tryosine phosphorylation of Tie2 in endothelial cells but does not induce endothelial cell chemotaxis or proliferation. However, Ang1 has been shown to induce the formation of capillary sprouts and promote survival of endothelial cells [44]. Overexpression of Ang1 results in more numerous and more highly branched vessels [45]. Targeted disruption of Ang1 is embryonic lethal and the defects in these mice resemble those in the Tie-2 deficient mice [45]. In addition to heart defects, there are a reduced number of vessels and remodeling of the initial primary capillary network does not occur. Importantly, there is a lack of recruitment of periendothelial supporting cells to the endothelial cells in Ang1-deficient mice, which leads to lack of blood vessel stabilization and maturation. A mutation in the tyrosine kinase domain of Tie2 has been linked to venous malformation, a pathology in which veins have a deficient amount of smooth muscle cells [46].

Ang1 is expressed embryonically, most prominently in heart myocardium. Later in development, Ang1 is associated with the mesenchyme surrounding developing vessels and in close association with endothelial cells [39]. It has been suggested that mesenchymal cells produce Ang1, which activates Tie2 on endothelial cells which in turn leads to the production and release of factors that recruit pericytes and smooth muscle cells, for example, PDGF-BB (reviewed in [4]).

Another member of the angiopoietin family has been described recently — angiopoietin-2 (Ang2) [47]. Ang2 is 60% identical to Ang1 but does not stimulate Tie2 tyrosine phophorylation. Ang2 might be a natural antagonist of Ang1 that blocks Ang1 activation of Tie2 and angiogenesis. Targeted overexpression of Ang2 in blood vessels resulted in vascular defects that resemble those in mice deficient in Ang1 or Tie2, presumably by inhibiting Ang1 function.

Fibroblast growth factor (FGF)

Acidic and basic fibroblast growth factor (FGF-1 and FGF-2, respectively), are very potent inducers of endothelial cell migration, proliferation and tube formation *in vitro* and are highly angiogenic *in vivo* (reviewed in [48]). The FGFs were among the first angiogenic factors to be well characterized and there is a large body of literature that describes FGF interactions with endothelial cells. Unlike VEGF and Ang1, however, an important role for FGFs in the development of the embryonic vasculature has not been demonstrated. This may be because, in contrast to VEGF, FGF is not a specific endothelial cell growth factor but is pleiotropic, and has many cell targets including smooth muscle cells and neurons. Nevertheless, based on their potency in inducing angiogenesis *in vivo*, FGFs are being used currently to stimulate collateral formation in ischemic limbs and hearts.

Therapeutic angiogenesis

Angiogenesis factors, such as FGF and VEGF, have the potential of augmenting collateral vessel development in myocardial and hindlimb ischemia (reviewed in [2]). In animal models, recombinant FGF-2 augmented collateral vessels in the lower limb of rabbits with acute hind limb ischemia and increased collateral vessel formation in dogs with infarcted myocardium. $VEGF_{165}$, both recombinant protein and cDNA, augmented collateral vessel formation in ischemic limbs. Angiogenesis factors are now being used clinically as a treatment for ischemia. For example, following treatment with $VEGF_{165}$ cDNA, improved blood flow to the ischemic limb has been observed in patients with rest pain and improved myocardial perfusion has been observed in patients with severe myocardial ischemia.

Inhibitors of angiogenesis

A number of angiogenesis inhibitors have been described recently (Figure 2). For example, there are natural molecules that apparently act directly on endothelial cells to block their migration, proliferation, and/or their ability to form capillary-like tubes. These include proteins such as angiostatin, endostatin, platelet factor-4, thrombospondin-1, interferon-α, tissue inhibitors of metalloproteineases, troponin I and others (reviewed in [3]). Several low molecular mass compounds that inhibit angiogenesis have been identified such as AGM 1470 [49] and thalidomide [50]. There also has been an effort to design inhibitors that intervene at various steps in the process of blood vessel formation (Figure 2). Examples are antibodies directed against VEGF, soluble receptors that sequester ligands and prevent access to VEGF and Tie receptors, VEGF receptor tyrosine kinase inhibitors, and antagonists of MMPs and integrin $\alpha_v\beta_3$. Some of these angiogenesis inhibitors with potential clinical application will be described here.

Thrombospondin-1

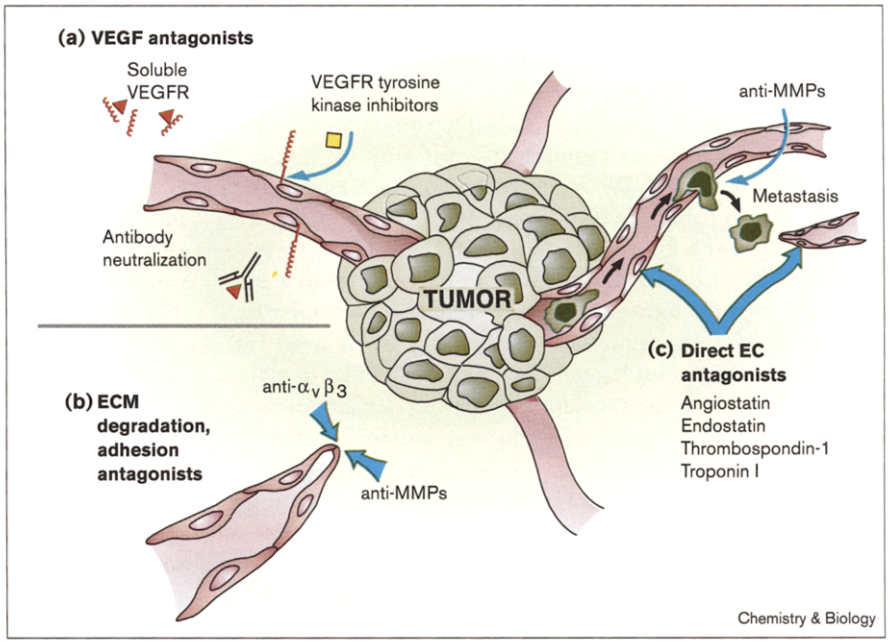
A 140 kDa fragment of thrombospondin-1 (TSP-1) was one of the first natural angiogenesis inhibitors to be described ([51]; reviewed in [1,3]). TSP-1 is an inhibitor of tumor growth and metastases in a number of animal models. Its expression is inversely correlated with angiogenic activity. For example, TSP-1 is down-regulated during tumorigenesis while angiogenesis activity is elevated [51]. In subsequent studies of fibroblasts cultured from patients with Li-Fraumeni disease, it was shown that TSP-1 is regulated by the *p53* tumor suppressor gene [52]. Loss of *p53* results in suppression of TSP-1 and a concomitant increase in angiogenic activity.

Angiostatin

Angiostatin is a 38 kDa internal fragment of plasminogen that encompasses the first four kringle domains of plasminogen [53]. It had been observed by clinicians that resection of certain primary tumors resulted in the rapid growth of previously dormant metastases. When a murine Lewis Lung carcinoma primary tumor was resected, distant lung metastases in these test mice grew significantly, in contrast to the control tumor-bearing mice, suggesting that the primary tumor produced an inhibitor of angiogenesis that suppressed growth of metastases, keeping them dormant. Angiostatin was purified from the serum and urine of these mice as an endothelial cell/angiogenesis inhibitor that blocked primary tumor growth and suppressed distant metastases in a variety of human tumors. Angiostatin enables micrometastases to remain dormant by increasing the tumor cell apoptotic rate. Whereas the rates of tumor cell proliferation in growing and dormant metastases were equivalent, the apoptotic rates in tumor cells were threefold higher in the dormant metastases [54]. Thus, tumor dormancy might be explained by a balance in tumor cell growth and death in the presence of angiogenesis promoters and suppressors. Tumor cells do not synthesize angiostatin directly, but may instead produce and secrete an as yet an unidentified enzyme that enters the circulation and interacts with plasminogen to release the angiostatin portion.

A recent report demonstrated that the ATP synthase F_1 complex is an angiostatin-binding protein [55]. This ATP synthase had previously been localized intracellularly to the mitochondria. It was speculated that when this enzyme is present on the surface of endothelial cells it may produce ATP which upon diffusion into the cell serves as an additional ATP source for endothelial cells. It

Figure 2



Processes in angiogenesis that are vulnerable to antagonists. **(a)** VEGF antagonists. VEGF is neutralized by specific anti-VEGF antibodies and sequestered by soluble receptors. Specific inhibitors of VEGF receptor tyrosine kinases inhibit VEGF-mediated signal transduction. **(b)** Antagonists of extracellular matrix (ECM) degradation, endothelial cell adhesion and migration. MMP inhibitors suppress enzyme activity preventing degradation of extracellular matrix and subsequent endothelial cell migration. Antibodies directed against integrin $\alpha_v\beta_3$ and cyclic RGD peptides block integrin $\alpha_v\beta_3$ function, thereby inhibiting endothelial cell adhesion to extracellular matrix and migration. **(c)** Natural antagonists interact with endothelial cells to block endothelial cell migration, proliferation and/or tube formation, thereby inhibiting tumor growth and metastasis. These antagonists include angiostatin, endostatin, thrombospondin-1 and troponin I. Metastasis, which requires tumor cell exit from blood vessels, can also be blocked by MMP inhibitors.

may be that angiostatin interferes with ATP production resulting in endothelial cell growth inhibition.

Endostatin

Endostatin is a 20 kDa carboxy-terminal fragment of collagen XVIII, purified from the conditioned media of hemangioendothelioma cells [56]. Like angiostatin, endostatin is a cryptic angiogenesis inhibitor released from a larger parent molecule that itself is not anti-angiogenic [3]. The identity of the enzyme that releases endostatin from collagen XVIII is unknown. Endostatin specifically inhibits capillary endothelial cell proliferation *in vitro* and is a potent inhibitor of the growth of primary and metastatic tumors [56–58]. Endostatin has several properties that suggest it might be of potential clinical use as an anti-angiogenic agent. One is that endostatin does not induce drug resistance as do conventional chemotherapy and radiation. In addition, in mouse tumor models, repeated cycles of administering and withdrawing systemic endostatin results in prolonged tumor dormancy without further treatment, suggesting that endostatin could completely suppress a tumor rather than just inhibit it transiently [59].

Troponin

Troponin I (TnI) is a recently described 22 kDa angiogenesis inhibitor isolated from cartilage [60]. Its discovery in cartilage as an anti-angiogenesis factor was unexpected because this protein is considered to be a muscle tissue-specific inhibitor of actomyosin ATPase, whose function is the Ca^{+2}-dependent regulation of muscle contraction as part of the troponin complex. TnI is an endothelial cell-specific inhibitor of FGF- and VEGF-driven capillary endothelial cell proliferation *in vitro* and of neovascularization in chorioallantoic membrane (CAM) and cornea models. TnI delivered systemically significantly inhibited lung metastases of murine B16-BL6 melanoma, a very aggressive variant of B16-F10 melanoma. Interestingly, TnI is used clinically as a sensitive serum marker to assess the degree of myocardial damage during infarction. It is speculated that the anti-angiogenic properties of TnI might be responsible for the difficulty in revascularizing ischemic myocardium following injury.

Inhibitors of VEGF, VEGF and Tie receptors

Several strategies have been developed to block VEGF action. For example, anti-VEGF antibodies decreased the vessel density and growth rate of several human tumors in nude mice but did not inhibit tumor cell growth *in vitro* [61]. More recently, humanized anti-VEGF monoclonal antibodies have been developed for clinical application that inhibit VEGF-induced endothelial cell proliferation and tumor growth [62]. Anti-VEGF antibodies have also been used to suppress iris neovascularization associated with retinal ischemia in nonhuman primates [63].

Soluble VEGF and Tie receptors have been explored as angiogenesis inhibitors with the rationale that they might sequester angiogenic ligands. A natural soluble Flt-1 receptor (sFLT-1), produced by endothelial and tumor cells has been identified as an alternative splice product that contains the first six of the seven amino-terminal

immunoglobulin-like domains of Flt-1 [64]. Soluble Flt-1 binds VEGF with high affinity and forms a heterodimeric complex with KDR. sFLT-1 protein inhibits VEGF-induced endothelial cell proliferation. Transfection of tumor cells with sFLT-1 resulted in reduced tumor growth and metastasis [65]. These results suggest that sFLT-1 acts as an angiogenesis inhibitor by sequestering VEGF and/or by acting as a dominant negative effector by forming heterodimers with transmembrane VEGFR tyrosine kinases. Soluble Flt-1 and Flk-1 receptors have been demonstrated to suppress retinal neovascularization in a murine model of ischemic retinopathy [66]. A similar experimental strategy has been used for Tie receptors. A soluble recombinant extracellular domain of Tie2 (ExTek.6His) substantially inhibited angiogenesis, tumor growth and metastases [67].

Another approach to inhibiting angiogenesis has been to inactivate receptors by inhibiting tyrosine kinase activity. SU5416 is a small synthetic compound that is a selective inhibitor of Flt-1/KDR tyrosine kinase. It inhibits VEGF-induced endothelial cell proliferation but not tumor-cell growth *in vitro* [68]. It also inhibits angiogenesis-dependent tumor growth and is now being evaluated in Phase I clinical trials.

Metalloproteinase inhibitors

The proteolytic degradation and remodeling of the extracellular matrix by migrating and proliferating capillary endothelial cells is one of the earliest and sustained events in angiogenesis. This process is mediated by MMPs and by serine proteases. Inhibition of MMPs is a potential therapeutic intervention site for anti-angiogenic therapies. An endogenous tissue inhibitor of metalloproteinases (TIMP) derived from cartilage was first shown to inhibit both embryonic and tumor-induced angiogenesis *in vivo* [69]. Subsequently, TIMP-1, TIMP-2 and TIMP-3 have been shown to have various anti-angiogenic activities (reviewed in [10]). These studies have led to the development of a number of synthetic metalloproteinase inhibitors, which are currently being tested in clinical trials against a variety of cancers including ovarian, lung and breast cancers.

Antagonists of $\alpha_v\beta_3$

Integrin $\alpha_v\beta_3$ expression is upregulated in endothelial cells as a response to endothelial cell growth factors such as FGF-2 and VEGF suggesting that it modulates endothelial cell migration and proliferation [12]. Disruption of integrin $\alpha_v\beta_3$ with anti-$\alpha_v\beta_3$ antibody or cyclic peptide antagonists of $\alpha_v\beta_3$, prevents new, but not pre-existing, blood vessel formation in angiogenesis model systems, in transplanted human skin and in tumors [11]. These $\alpha_v\beta_3$ antagonists are currently in clinical trials as a treatment for cancer. Interestingly, proteolytic and cell adhesion events may be linked in the regulation of angiogenesis. Integrin $\alpha_v\beta_3$ binds directly to MMP-2 on the surface of invading endothelial cells thereby facilitating the cell-surface localization of this enzyme as well as potentiating its cell-mediated extracellular matrix degradation. During angiogenesis, however, a noncatalytic carboxy-terminal hemopexin-like domain of MMP-2 (known as PEX) is generated that blocks integrin–MMP-2 interactions, resulting in suppression of collagenolytic activity and the inhibition of angiogenesis and tumor growth [70]. These events may constitute a feedback system that eventually down-regulates angiogenesis after the initial stimulus.

Conclusions and prospects

Interest in angiogenesis has grown dramatically in recent years for several reasons. One is the identification of angiogenesis factors such as VEGF, angiopoietin and their receptors, factors that play a key role in regulating angiogenesis. A series of targeted gene 'knockout' studies in mice and other approaches have begun to elucidate the mechanisms by which these molecules contribute to the vasculogenic and angiogenic processes during development. Secondly, a strong clinical interest has emerged in developing anti-angiogenesis reagents as therapeutic strategies for inhibiting tumor growth and metastasis, as well as a variety of ocular pathologies. Angiogenesis factors such as VEGF and FGF also have clinical utility in promoting therapeutic angiogenesis in ischemic disease. It is anticipated that the mechanisms by which angiogenic modulators exert their effects will become better understood and that a new generation of potent drugs capable of promoting or inhibiting angiogenesis will be developed.

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