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REVIEW ARTICLE

Angiogenic targets for potential disorders

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ABSTRACT

This review shall familiarize the readers with various fundamental aspects of angiogenesis. Angiogenesis is a feature of a limited number of physiological processes like wound healing, ovulation, development of the corpus luteum, embryogenesis, lactating breast, during immune response, and during Inflammation. It is driven by a cocktail of growth factors and pro-angiogenic cytokines and is tempered by an equally diverse group of inhibitors of neovascularization. The properties and biological functions of angiogenic growth factors such as VEGF, FGF-2, nitric oxide, MMP, angiopoietin, TGF-β as well as various inhibitors such as angiostatin, endostatin, thrombospondin, canstatin, DII4, PEDF are discussed in this review with respect to their impact on angiogenic process. In recent years, it has become increasingly evident that excessive, insufficient, or abnormal angiogenesis contributes to the pathogenesis of many more disorders. A long list of disorders is characterized or caused by excessive or insufficient angiogenesis whereas several congenital or inherited diseases are also caused by abnormal vascular remodeling. It may be possible in the future to develop specific anti-angiogenic agents that offer a potential therapy for cancer and angiogenic diseases.

INTRODUCTION

Angiogenesis, the formation of new vascular segments originating from existing vessels is characterized by a combination of sprouting of new vessels from the sides and ends of pre-existing ones or by longitudinal division of existing vessels with periendothelial cells (intussusception), either of which may then split and branch into pre-capillary arterioles and capillaries [1]. Angiogenesis requires many interactions that must be tightly regulated in a spatial and temporal manner. This process is regulated by a wide range of angiogenic inducers, including growth factors, chemokines, angiogenic enzymes, endothelial-specific receptors, and adhesion molecules as well as various endogenous angiogenesis inhibitors like angiostatin, endostatin, thrombospondin, canstatin, PEDF [2]. Imbalances between the angiogenic inducers and inhibitors may result in pathologies such as cancer, arthritis, psoriasis, obesity, asthma, atherosclerosis, infectious disease, heart and brain ischemia, neurodegeneration, hypertension, pre-eclampsia, respiratory distress, osteoporosis, and many other disorders. Several congenital or inherited diseases are also caused by abnormal vascular remodeling [3]. As the imbalance between various angiogenic mediators causes different pathologies, they may be the targets for therapeutic intervention in these disorders. This review discusses the role and regulation of various key inducers and inhibitors of angiogenesis as well as gives an overview of variety of disorders involving either excessive or insufficient angiogenesis.

ANGIOGENESIS

Angiogenesis is a feature of a limited number of physiological processes. It is found to occur in the female reproductive system during ovulation, development of the corpus luteum, embryogenesis, lactating breast, during immune response, and during Inflammation and wound repair [4]. In contrast, the etiology and pathogenesis of a much larger and increasingly expanding number of pathologic conditions have been

shown to be a consequence of an angiogenic response that is persistent either because of the overproduction of normal or aberrant forms of angiogenic mediators, or because of a relative deficiency in inhibitors of this process.

Angiogenic process occurs by two or combination of the two processes, i.e. sprouting or intussusceptions, which then splits and branches into capillaries. The molecular basis of angiogenesis is most easily characterized by viewing the process as a step-wise progression [5] (*Figure 1*)

1 Existing vessels dilate, vascular permeability increases, and extracellular matrix (ECM) is degraded by an array of proteases. This degradation of ECM provides room for the migrating endothelial cells.
2 Endothelial cells proliferate and migrate.
3 Endothelial cells assemble, form cords, and acquire lumen.
4 Long-term survival of vascular endothelium.
5 Vascular endothelium differentiates to meet local needs.
6 Remodeling of vessels yields complex, functional networks forming either an artery or a vein.

Angiogenesis inducers

Angiogenesis is a complex process involving extensive interplay between cells, soluble factors, and ECM components [2]. The majority of the stimulatory molecules are proteins, and many of them are growth factors that induce endothelial cells to divide, migrate directionally toward the inducing stimulus, and differentiate into tubular structures. Most are secreted by a variety of cells,

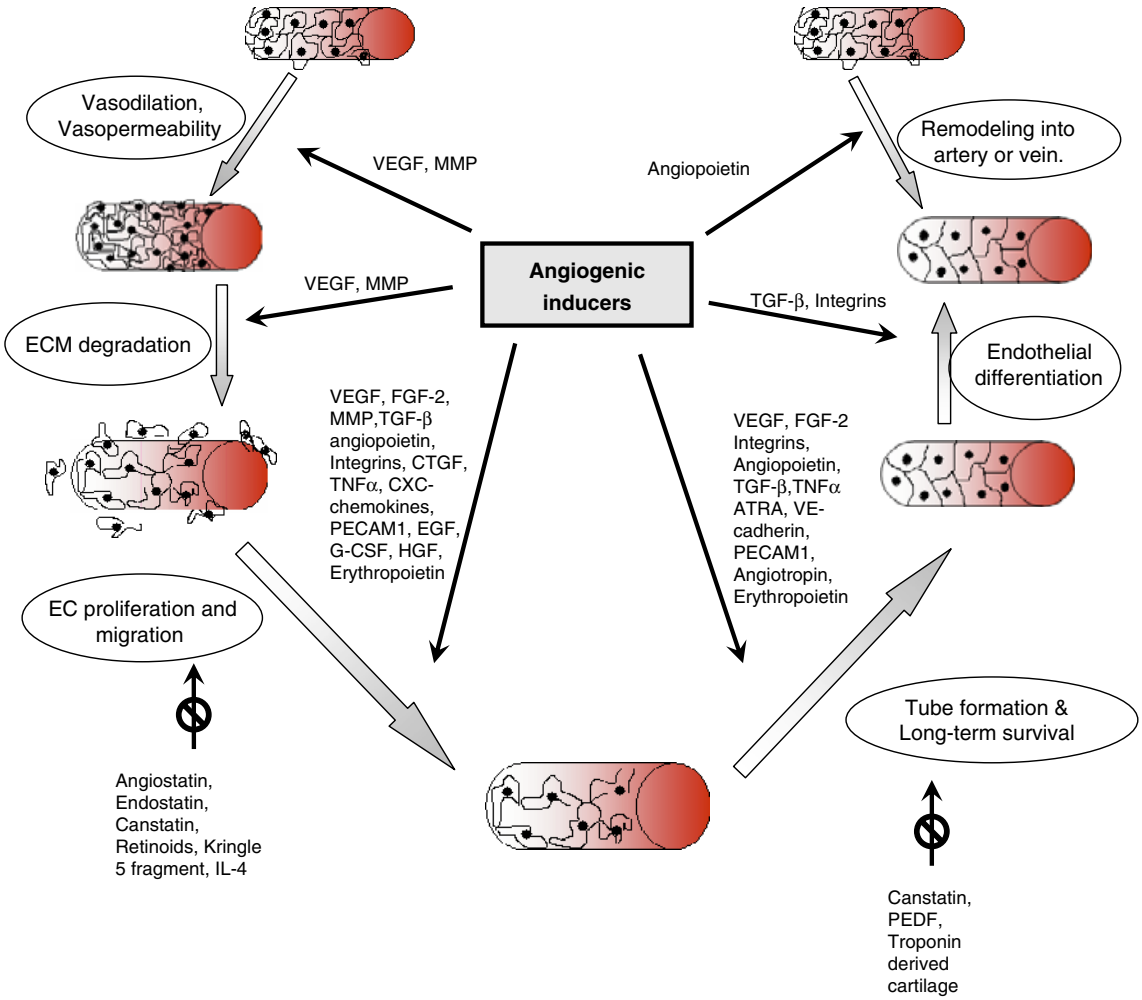

Figure 1 Step-wise angiogenic process alongwith site of action of various angiogenic inducers and inhibitors.

including endothelial cells themselves, in response to exogenous or endogenous stimuli and are produced locally and function in an autocrine and/or paracrine manner. These mediators can stimulate angiogenesis directly by interacting with receptors on the endothelial cell surface, or indirectly by attracting and activating accessory cells, i.e. inflammatory macrophages, and inducing them to produce angiogenic mediators. Still others play a key role in stabilizing and/or enhancing the function of stimulatory molecules normally sequestered in the ECM surrounding blood vessels, as heparin does, which when bound to basic fibroblast growth factor facilitates its interaction with high-affinity receptors on the endothelial cell surface [6].

Mechanical stimulators

Mechanical stimulators of angiogenesis are not well characterized. There is a significant amount of controversy with regard to shear stress acting on capillaries to cause angiogenesis, although current knowledge suggests that increased muscle contractions may increase angiogenesis. This may be because of an increase in the production of nitric oxide during exercise. [7].

Chemical stimulators

The chemical stimulators of angiogenesis have various biological functions affecting different steps in the process of angiogenesis (*Table I*). Their implications in various angiogenic disorders are discussed as follows:

1 Vascular endothelial growth factor (VEGF)
Vascular endothelial growth factor is a potent mitogen of endothelial cells that has been implicated in the angiogenic response to exercise. VEGF is primarily upregulated in the fibers that undergo angiogenesis. Upregulation of VEGF mRNA has been shown to occur during exercise in humans, in both normal healthy individuals and also in patients with heart failure [7]. VEGF was detected in synovial fluids from patients with active rheumatoid arthritis (RA), and VEGF mRNA was found to be expressed by RA lining layer cells and synovial macrophages [8,9]. It was detected in the ovary during corpus luteum formation and in the uterus during growth of endometrial vessels and at the site of embryo implantation. Also, high VEGF levels were detected during the proliferative phase of wound healing. VEGF is equally detectable in areas where endothelial cells are quiescent, such as heart, lung, and brain, pointing to the role of VEGF as a survival factor. Additionally, VEGF is thought to play a role in several human cancers, diabetic retinopathy, and atherosclerosis [2].

2 Hypoxia-inducible factor (HIF-1)
The presence of HIF-1α mRNA and subsequently the presence of VEGF mRNA in the heart tissue of patients with infarction provide compelling new evidence that HIF-1α contributes to limitation of infarct size by promoting angiogenesis and vascular remodeling and that it does so by increasing steady-state levels of VEGF mRNA [10].

3 Nitric oxide (NO)
Endothelium-derived NO is a mediator of angiogenesis. NO is an endothelial survival factor, inhibiting apoptosis and enhancing endothelial cell proliferation [11].

4 Placenta-derived growth factor (PLGF)
Placenta-derived growth factor stimulates the formation of vessels in ischemic heart disease. PLGF plays a critical part in the recruitment and homing of circulating endothelial progenitor cells (CEPs) and supports monocyte recruitment for vasculogenesis at the site of ischemia and in tumors [12].

5 Basic Fibroblast Growth Factor (FGF-2)
Mice lacking FGF-2 show neuronal defects and delayed wound healing. Furthermore, FGF-2 is produced by many tumor cell lines in vitro and is thought to play a role in the growth and neovascularization of solid tumors. High levels of FGF-2 are present in endothelial cells of Kaposi's sarcoma and in proliferating hemangiomas, and elevated amounts of FGF-2 have been detected in the serum and urine of patients with advanced colorectal, breast, ovarian, and renal carcinomas and soft tissue sarcoma [2].

6 Matrix metalloproteinase (MMP)
Excessive MMP activity has been detected in colorectal, lung, breast, gastric, cervical, bladder, prostate cancer, and malignant glioblastoma. Moreover, in number of studies, a good correlation was found between the amount of MMPs and the aggressiveness/invasiveness of the tumor [13].

7 Angiopoietins
The angiogenic factor, angiopoietin (Ang)-1 is an agonist ligand of the endothelial receptor tyrosine kinase Tie-2 [14]. Several molecules named as angiopoietin-related proteins (ARPs) or angiopoietin-like proteins (Angptls) are structurally similar to angiopoietin but do not bind to Tie-2 receptors. ARPs/Angptls show pleiotropic effects not only on vascular cells but also on cells of other lineages, such as skin and chondrocyte cells [15]. More recent

Table I List of angiogenic inducers.

Angiogenic inducers	Biological function	References
Vascular endothelial growth factor (VEGF)	Stimulates ECM degradation, proliferation, migration, and tube formation of endothelial cells in vitro and regulate vascular permeability in vivo	Liekens et al. 2001 [2]
Hypoxia-inducible factor (HIF-1)	Transcriptional activator of VEGF, inducible nitric oxide synthase, lactate dehydrogenase, and erythropoietin	Lee et al. 2000 [10]
Nitric oxide (NO)	Enhances endothelial cell proliferation, in part by increasing the expression of VEGF or fibroblast growth factor, enhances endothelial migration. Also suppress the production of angiostatin	Cooke and Losordo 2002, Matsunaga et al. 2002 [11,104]
Placenta-derived growth factor (PLGF)	Bind both VEGFR-1 and VEGFR-2 and stimulates the formation of vessels	Gupta and Zhang 2005 [12]
Basic- Fibroblast Growth Factor (FGF-2)	Potent inducers of endothelial cell migration, proliferation, and tube formation	Klagsbrun and Moses 1999 [42]
Matrix metalloproteinase (MMP)	Endothelial cell invasion and migration	Mignatti and Rifki 1996 [105]
Angiopoietins	Survival and migration of endothelial cells and regulates vascular remodeling, stabilizes vessels by maximizing the interactions between endothelial cells	Morisada et al. 2006, Thurston et al. 1999 [16,106]
Angiogenin	Exhibit ribonucleolytic activity, binds with high-affinity to endothelial cell-surface receptors and, with lower affinity, to extracellular matrix (ECM)	Wiedlocha 1999 [107]
Thymidine phosphorylase	Promotes endothelial tubulogenesis in vitro *and* development of functional vasculature into an avascular sponge in vivo	Sengupta et al. 2003 [108]
Carbonic Anhydrase 9	Linked to expression of a constellation of proteins involved in angiogenesis, apoptosis inhibition, growth intensification, and cell–cell adhesion disruption	Giatromanolaki et al. 2001 [19]
Cyclo-Oxygenase 2 (COX 2)	Co-expression of VEGF and transforming growth factor ß (TGF-ß) associated with increased tumor microvascular density and proliferation of new vessels	Fosslien 2001 [21]
Connective tissue growth factor (CTGF)	Mediate cell adhesion, stimulate cell migration, and augment growth factor-induced DNA synthesis, mediator of transforming growth factors β	Kireeva et al. 1997, Holmes et al. 2001 [109,110]
Transforming growth factor (TGF-β)	Regulator of proliferation, migration, survival, differentiation, and ECM synthesis in endothelial cells and vascular smooth muscle cells and maintenance of vascular homeostasis	Bertolino et al. 2005 [111]
Tumor Necrosis Factor α	Promotes EC migration and tube formation in low doses and have inhibitory effects in higher doses, formation of new vessels in vivo	Distler et al. 2003 [27]
CXC-Chemokines	Members with ELR motif promotes EC proliferation and migration. Members, which lack ELR motif inhibit angiogenesis	Distler et al. 2003 [27]
Integrins	Interaction with the ECM necessary for cell adhesion, migration and positioning, and induce signaling events essential for cell survival, proliferation, and differentiation	Curzio et al., 2004 [22]
Interleukins	IL-1α promotes angiogenesis by activating the VEGF-VEGFR-2 signaling pathway IL-8 has direct angiogenic effects on EC	Salven et al. 2002, Heidemann et al. 2003 [35,36]
VE-cadherin	Reduce EC apoptosis, promotes vessel stabilization	Distler et al. 2003 [27]
Platelet endothelial cell adhesion molecule 1 (PECAM 1)	EC migration, tube formation, EC aggregation, vessel stabilization	Distler et al. 2003 [27]
Epidermal growth factor (EGF) & transforming growth factor α (TGF- α)	EC proliferation, reduce EC apoptosis	
Vitamin K Epoxide Reductase (VKOR)	Upregulated in many tissues under angiogenesis-related physiologic conditions such as in fetal heart and in pathologic conditions such as ventricular aneurysm caused by myocardial infarction and tumor	Wang et al. 2005 [40]

Table I (*Continued*).

Angiogenic inducers	Biological function	References
Retinoids	Induces capillary tube formation via retinoic acid receptor mainly by stimulation of human umbilical vein endothelial cell proliferation and enhancement of endogenous VEGF signaling and in part by induction of hepatocyte growth factor and angiopoietin-2 production	Saito et al. 2007 [41]
G-CSF and GM-CSF	EC migration and proliferation	Bussolino et al. 1989 [112]
Angiotropin	Promotes tube formation	Hockell et al. 1988 [113]
Insulin-like growth factor	Induction of VEGF and Plasminogen activators	Oh et al. 2002 [114]
Hepatocyte growth factor	EC migration and proliferation. Induces EC apoptosis	Matsumoto and Nakamura 1996 [115]
Erythropoietin	EC proliferation and tube formation. Induces EC apoptosis	Ashley et al. 2002, Yasuda et al. 2002 [116,117]

studies have proposed that ARPs/Angptls are involved in various pathologies, such as tumor angiogenesis and metabolic diseases [16].

8 Angiogenin

Inhibition of the action of angiogenin may prove to be an effective therapeutic approach for the treatment of malignant disease [17].

9 Thymidine phosphorylase

Platelet-derived endothelial cell growth factor (now known as thymidine phosphorylase) was described as a mitogenic and angiogenic factor present in platelets [18]. Thymidine phosphorylase is elevated in the plasma of cancer patients and has been implicated in pathophysiological angiogenesis. Thymidine phosphorylase and its ribose-sugar metabolites induce angiogenesis by mediating a cohesive interplay between carcinoma and endothelial cells.

10 Carbonic Anhydrase 9

Carbonic Anhydrase 9 is expressed by many tumor types, e.g: cervical, esophageal, colorectal, and lung cancer but it seems to be rarely expressed in normal tissues. Carbonic Anhydrase inhibitors may suppress tumor invasive growth and, furthermore, enhance the cytotoxicity of several chemotherapeutic agents [19].

11 Cyclo-Oxygenase 2 (COX 2)

Cyclo-oxygenase 2 is the rate-controlling enzyme in prostaglandin (PG) synthesis. COX-2 activity is known to be upregulated in the rheumatoid arthritis (RA) synovium. COX-2-induced angiogenic activity is an active mechanism within diseased synovium and may provide an additional rationale for the use of COX-2 inhibitors in RA [20]. Colon cancer, the malignant cells, the stromal fibroblasts, and the endothelial cells all exhibit strong staining for cyclo-oxygenase-2 [21]. COX-2 and VEGF expression are elevated in breast and prostate cancer tissues and their cell lines. Chronic intake of nonsteroidal anti-inflammatory drugs and COX-2 inhibitors significantly reduces the risk of cancer development, and this effect may be due, at least in part, to the inhibition of tumor angiogenesis [22].

12 Connective tissue growth factor (CTGF)

Connective tissue growth factor is a major inducer of ECM production in fibrotic diseases, which are characterized by excessive collagen deposition. CTGF is over expressed in fibrotic lesions, and the degree of over expression correlates with severity of disease [23,24]. CTGF may participate in wound repair by acting as angiogenic inducers upon endothelial cells and by acting as chemotactic, proliferative, and matrix remodeling factors upon fibroblasts [25]. The hypoxic induction of angiogenesis by human breast cancer cells (MDA-231) can be ascribed at least in part to CTGF. CTGF may stimulate angiogenesis by paracrine mechanisms, thereby contributing to the invasion of breast cancer cells [26].

13 Transforming growth factor (TGF-β)

Transforming growth factor-β can act as an angiostatic (higher doses) or angiogenic (Lower doses) molecule [27]. In the cardiovascular system, TGF-β has the ability to influence cell proliferation, migration, apoptosis, and the accumulation of ECM. Consequently, it has been implicated in restenosis after angioplasty, the pathogenesis of atherosclerosis, arteriogenesis and angiogenesis, and a variety of cardiovascular fibrotic disorders [28].

14 Tumor Necrosis Factor α (TNF-α)

Tumor Necrosis Factor-α accelerates wound epithelialization and neovascularization in an in vivo wound healing model. [29]. Another study indicated that it upregulates angiogenic factor expression in

malignant glioma cells [30]. Moreover, inhibition of TNF-α significantly improves vascular recovery within ischemic tissue and reduces pathological neovascularization in ischemic retinopathy [31]. Recently, Pucci et al. [32] found the association of angiogenesis and tumor necrosis factor α with macrophage infiltration in coronary artery aneurysms of a fatal infantile Kawasaki disease (infantile febrile illness characterized by systemic vasculitis).

15 CXC-Chemokines

Members that contain the ELR motif (3 amino acids – Glu–Leu–Arg) are potent promoters of angiogenesis. In contrast, members that are inducible by interferons and lack the ELR motif are potent inhibitors of angiogenesis [27]. The CXC chemokines appear to be important in the regulation of angiogenesis associated with the pathogenesis of chronic inflammatory/fibroproliferative disorders. And thus therapy directed at either inhibition of angiogenic or augmentation of angiostatic CXC chemokines may be a novel approach in the treatment of chronic fibroproliferative disorders [33]. Also, CXC chemokines display pleiotropic effects in immunity, regulating angiogenesis, and mediating organ-specific metastases of cancer [34].

16 Integrins

Anti-integrin antibodies and small molecular integrin inhibitors suppress angiogenesis and tumor progression in many animal models and are currently tested in clinical trials as anti-angiogenic agents [22].

17 Interleukins

Interleukins-1α may play a role in several acute and chronic conditions with increased angiogenesis and/or vascular permeability like cancer, infections, inflammatory disorders including rheumatoid arthritis, and vascular events such as atherosclerotic plaque development [35]. IL-8 exerted a more pronounced chemotactic effect on dermal microvascular EC compared to macrovascular EC [36]. Increased IL-6 expression was measured in vivo during the formation of the vascular system that accompanies development of ovarian follicles following embryo implantation. In a wound healing model, increased IL-6 protein was found in wound fluid and serum within 12 hrs after wounding. Both tumor growth and systemic inflammation were reduced in a mouse cancer model treated with IL-6 antibodies. These suggest that both IL-6 and inflammation are part of the angiogenic process. Furthermore, IL-6 might play a role in lung angiogenesis after ischemia [37].

18 Vascular Endothelial-cadherin (VE-cadherin)

Rabascio et al. [38] indicated that the quantitative evaluation of circulating VE-cadherin RNA is a specific and highly promising tool with which to investigate the angiogenic phenotype of cancer patients. VE-cadherin is found to be a preferable marker for assessing microvessels and angiogenesis in human breast cancer [39].

19 Platelet endothelial cell adhesion molecule 1 (PECAM 1)

It plays a role in leukocyte migration at the sites of inflammation, T-cell activation, platelet aggregation, and angiogenesis. Also, by blocking the antibodies directed against PECAM-1 cytokine and tumor-induced angiogenesis was abolished in vivo [27].

20 Epidermal growth factor (EGF) & transforming growth factor α (TGF-α)

Treatment with antibodies blocking the activation of EGF receptor signaling pathway in cancer cells results in increased apoptosis of endothelial cells and decreased vascular density. TGF-α themselves are mitogenic for endothelial cells [27].

21 Vitamin K Epoxide Reductase (VKOR)

Vitamin K Epoxide Reductase may have roles in physiologic and pathologic angiogenesis. It participates in the development of angiogenesis-related pathologic conditions such as tumorigenesis and ischemic cardiovascular diseases [40].

22 Retinoids

Retinoids have been reported to possess anti-angiogenic properties. But on the other hand, all trans retinoic acid have been reported to be beneficial for atherosclerotic vascular disorders by inducing differentiation and inhibiting proliferation in vascular smooth muscle cells. Retinoids may therefore be potential candidates for therapeutic angiogenesis against ischemic vascular disorders [41].

23 Miscellaneous

Many other molecules like granulocyte and granulocyte/macrophage colony-stimulating factor, angiotropin, insulin-like growth factor, hepatocyte growth factor, erythropoietin have been linked to angiogenesis but their roles are less well characterized. (Refer *Table I*).

Angiogenesis inhibitors

A number of angiogenesis inhibitors have been described recently. 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 [42]. It is now recognized that at least two endogenous molecular barriers defend against pathological hotspots of angiogenesis: (i) angiogenesis inhibitors in the host such as tetrahydrocortisol, platelet factor 4, angiostatin, and endostatin; and (ii) angiogenesis inhibitors expressed by normal cells, but downregulated during the switch to the angiogenesis phenotype in tumor cells, such as thrombospondin [43]. The biological functions of the various angiogenic inhibitors are described in *Table II*. Their implications in various disorders are discussed in the following:

1 Thrombospondin

Thrombospondin-1 is an inhibitor of tumor growth and metastases in a number of animal models. Because of the large size (450 kDa), poor bioavailability, and proteolytic breakdown, clinical use of thrombospondin is limited. However, ABT-510, a mimetic peptide sequence of thrombospondin possessing anti-angiogenic activity is in phase II clinical trials [12].

2 Angiostatin

Angiostatin was purified as an endothelial cell/angiogenesis inhibitor that blocked primary tumor growth and suppressed distant metastases in a variety of human tumors [42].

3 Endostatin

It is a potent inhibitor of the growth of primary and metastatic tumors. Endostatin has several properties that suggest it might be of potential clinical use as an anti-angiogenic agent such as it does not induce drug resistance as do conventional chemotherapy and radiation. Endostatin could completely suppress a tumor rather than just inhibit it transiently as shown in some mouse tumor models [42].

4 Canstatin

In vivo experiments show that it significantly inhibits solid tumor growth. The canstatin-mediated inhibition of tumor is related to apoptosis [44].

5 Delta-like ligand 4(DII4)

Lobov et al. [45] reported that during normal retinal vascular development, and in the oxygen-induced ischemic retinopathy model, suppression of Dll4/Notch signaling markedly enhanced angiogenic sprouting and promoted the formation of a denser primary capillary network.

Table II List of angiogenic inhibitors.

Angiogenic inhibitor	Biological function	References
Thrombospondin	Prevented VEGF-induced angiogenesis by directly binding to it and by interfering with its binding to cell surface heparan sulfates	Gupta and Zhang 2005 [12]
Angiostatin	Interferes with ATP production resulting in endothelial cell growth inhibition, anti-migratory, and anti-proliferative activities	Liekens et al. 2001, Klagsbrun and Moses 1999 [2,42]
Endostatin	Inhibits capillary endothelial cell proliferation	Klagsbrun and Moses 1999 [42]
Canstatin	Inhibit specifically endothelial cell proliferation, migration, and tube formation via a cell surface protein/receptor. Also induces endothelial cell apoptosis associated with phosphatidylinositol 3-kinase/Akt inhibition	Ying et al. 2004 [44]
Delta-like ligand 4(DII4)	VEGF induces Dll4 expression as part of a negative regulatory loop in which Dll4 acts as a potent endogenous inhibitor of vascular sprouting	Lobov et al. 2007 [45]
Chondromodulin-I	Regulate the vascular invasion during endochondral bone formation	Hayami et al. 2003 [46]
Heparinases	Depletion of heparan sulfate receptors that are critical for growth factor-mediated endothelial cell proliferation and hence inhibits neovascularization	Sasisekharan et al. 1994 [47]
Kringle 5 fragment	Inhibits endothelial cell proliferation. The recombinant kringle 5 of human plasminogen inhibits endothelial cell migration also	Ji et al., 1998 [49]
Pigment epithelial-derived factor (PEDF)	Blocks angiogenesis by inducing endothelial cell death, also blocks basic fibroblast growth factor (bFGF) and VEGF-induced transcription	Filleur et al. 2005 [52]
Retinoids	Inhibition of cell proliferation and differentiation, decrease in VEGF expression by keratinocytes	Lachgar et al. 1999 [54]
Troponin-derived cartilage	Inhibit endothelial cell tube formation as well as endothelial cell division and reduces VEGF production	Beatrice et al. 2003 [55]
Interferons	Inhibit secretion of angiogenic factors such as basic FGF, Interferon γ–inducible protein affects endothelial cells with respect to apoptosis and proliferation	Lindner 2002, Feldman et al. 2006 [57,118]
Interleukins	IL-4 inhibits endothelial cells migration, IL-12 induce IFN γ, promotes apoptosis of endothelial cells	Volpert et al. 1998, Akhtar et al. 2004 [58,59]

6 Chondromodulin-I

Chondromodulin-I (ChM-I), a cartilage-derived anti-angiogenic factor, has been shown to regulate the vascular invasion during endochondral bone formation. High expression of ChM-I was detected in articular cartilage of growing and normal adult joints, implicating its role in the maintenance of avascularity of intact articular cartilage. The loss of ChM-I from articular cartilage might be responsible in part for promoting blood vessel invasion into the cartilage during progression of osteoarthritis [46].

7 Heparinases

The heparin-degrading enzymes, heparinases I and III, but not heparinase II, inhibited both neovascularization in vivo and proliferation of capillary endothelial cells mediated by basic fibroblast growth factor in vitro [47]. In another study, the intramuscular injection of heparinase in white rabbits improves perfusion to the ischemic limb through the process of enhanced collateral vessel development. The angiogenic effect of heparinase on the ischemic tissue may result from release of endogenous angiogenic factors, such as bFGF [48].

8 Kringle 5 fragment

Kringle 5 fragment shows selective inhibition on endothelial cells as opposed to other cell types [49]. It has promise in anti-angiogenic therapy because of its small size and potent inhibitory effect [50].

9 Pigment epithelial-derived factor (PEDF)

Pigment epithelial-derived factor is one of the known anti-angiogenesis factors and is naturally occurring in the body [51]. Studies of retinopathy and macular degeneration show that PEDF suppresses angiogenesis and vascular leakage in the eye. PEDF suppresses tumor growth in neuroectodermal tumors, mouse melanoma, and ovarian cancer. Forced PEDF expression delays the growth and invasion of lung carcinoma, hepatocellular carcinoma, melanoma, and glioblastoma, where it blocks neovascularization. Moreover, decreased PEDF levels in the metastatic prostate adenocarcinoma in rat and humans, compared with the nonmetastatic disease imply that the loss of PEDF contributes to the progression to a metastatic phenotype. PEDF is repressed by testosterone in the cultured prostate epithelium and increased in the prostate in vivo upon castration, suggesting that PEDF is as a key hormone-regulated angiogenesis inhibitor in this organ [52]. PEDF is an important factor in non small cell lung carcinoma (NSCLC) development and may be of prognostic value for NSCLC patients [51].

10 Retinoids

Retinoids have been reported to possess anti-angiogenic properties. Retinoids combined with interferon α-2a (IFNα) or 1, 25-dihydroxyvitamin D_3 [1, $25(OH)_2D_3$] have shown marked synergistic inhibitory effects on angiogenesis induced by tumor cell lines harboring DNA of oncogenic human papillomaviruses (HPV) type 16 or 18. This provides a further basis for the use of combinations of retinoids with IFNα or $1,25(OH)_2D_3$ in the treatment of angiogenesis-dependent malignancies [53]. The decrease in VEGF expression by keratinocytes on contact with retinoids may prevent skin neoangiogenesis in certain skin diseases [54]. Therapeutic applications of all trans retinoic acid and its derivatives against various malignancies have been increasing.

11 Troponin-derived cartilage

Troponin I is one of the several inhibitors of angiogenesis identified in bovine and shark cartilage. The active site of troponin I was found to significantly inhibit endothelial cell tube formation as well as endothelial cell division. It was also found to reduce VEGF production [55]

12 Interferons

Interferon-alpha (IFN-α) has been shown to inhibit angiogenesis both in vivo and in human neonatal hemangiomas. It has been shown to diminish the primary and secondary incidence of hepatocellular carcinoma in patients with preserved liver function [56]. The anti-angiogenic activity of IFNs is enhanced when they are combined with other anti-angiogenic agents, such as tamoxifen and thalidomide [57].

13 Interleukins

Interleukins-4 secreting cells inhibit the growth of distant tumors. The local anti-angiogenic activity of IL-4 causes decrease in tumor vessel density observed in IL-4 secreting gliomas and enhance its effectiveness as a gene therapy agent against tumor metastases. The inhibition of angiogenesis may also play a role in the ability of IL-4 to ameliorate arthritis in animals and reduce the cartilage degradation in patients that results in part from invading endothelial cells in the synovial pannus [58]. IL-12 affects endothelial cell growth through various mechanisms hence it is particularly interesting for the suppression of endothelial cell growth in many cancers [59]. IL-12 can be effectively delivered using a gene-based approach with a heat shock promoter, which results in quantitatively measurable anti-angiogenesis and general immunostimulation in many tumors [60].

Angiogenesis in various disorders

Historically, angiogenesis was implicated only in cancer, arthritis, and psoriasis. In recent years, it has, however, become increasingly evident that excessive, insufficient, or abnormal angiogenesis contributes to the pathogenesis of a long list of disorders (*Table III and IV*).

Diseases characterized by insufficient angiogenesis

Insufficient vessel growth and abnormal vessel regression not only cause heart and brain ischemia, but can also lead to neurodegeneration, hypertension, pre-eclampsia, respiratory distress, osteoporosis, and many other disorders. The angiogenic mechanisms of such disorders are given in *Table III*.

1 Myocardial Ischemia

Therapeutic modulation of angiogenesis represents an interesting frontier of cardiovascular medicine. Formation of new vessels on the ischemic heart or other tissues would be an important clue in the treatment of disorders for which medical intervention or surgical therapy like percutaneous coronary intervention and coronary artery bypass surgery turned out to be ineffective. This strategy is designed to promote the development of supplemental collateral blood vessels that will act as endogenous bypass conduits [61]. The goal of treatment is both relief of symptoms of coronary artery disease and improvement of cardiac function by increasing perfusion to the ischemic region. Protein-based therapy with cytokines including VEGF and fibroblast growth factor demonstrated functionally significant angiogenesis in several animal models [62]. Initial phase I and II clinical trials results are encouraging and reflect the potential success of therapeutic angiogenesis as a clinical modality for the treatment of ischemic heart disease [63]. Various early clinical trials of therapeutic angiogenesis have shown reduction in anginal symptoms and increases in exercise time, as well as objective evidence of improved perfusion, left ventricular function, and angiographic appearance following such angiogenic treatments [64]. However, some clinical trials have yielded largely disappointing results. The attenuated angiogenic response seen in clinical trials of patients with coronary artery disease may be because of multiple factors including endothelial dysfunction, particularly in the context of advanced atherosclerotic disease and associated comorbid conditions, regimens of single agents, as well as inefficiencies of current delivery methods. It is likely the optimal treatment will involve multiple agents as angiogenesis is a complex process involving a large cascade of cytokines, as well as cells and ECM, and administration of a single factor may be insufficient [62]. In the future, angiogenesis will likely be offered as an adjunct to conventional revascularization strategies in subsets of patients who are only 'suboptimally' revascularized with conventional techniques and might evolve into a stand-alone treatment for some patients with nonrevascularizable disease.

2 Myocardial Hypertrophy

Myocardial hypertrophy is associated with progressive contractile dysfunction, increased vulnerability to ischemia–reperfusion injury, and is, therefore, a risk factor in cardiac surgery. Promoting angiogenesis proved useful in preserving myocardial function in late hypertrophy and improving post-ischemic recovery of contractile function [65].

3 Hypertension

A reduced density of arterioles and capillaries is an important common characteristic of various microvascular beds in many forms of hypertension. Emerging evidence supports a novel view of hypertension as a disease of inadequate or aberrant responses to angiogenic growth factors. A major side effect of bevacizumab, a monoclonal antibody to VEGF, is hypertension. Pre-eclampsia is accompanied by high circulating levels of soluble VEGF receptor-1, which forms inactive complexes with VEGF and placental growth factor [66]. Paradoxically, early studies have demonstrated high circulating levels of angiogenic growth factors in hypertension. Several mechanisms may account for this finding including increased vascular stretch, tissue ischemia, compensatory responses, decreased clearance, or a combination of these mechanisms. High angiogenic growth factors in hypertension could contribute to clinical sequelae such as peripheral and pulmonary edema, microalbuminuria, and progression of atherosclerosis. However, a role for altered angiogenesis in the pathogenesis of hypertension or its sequelae has not been established. Novel studies to understand the roles of angiogenic growth factors in hypertensive patients are warranted [67].

4 Atherosclerosis

Atheromatous lesions, beyond a certain size, contain an increased number of vasa, indicating that intimal angiogenesis occurs as part of an adaptive change known as vascular remodeling [68]. The role of angiogenesis in destabilization and rupture of athero-

Table III Diseases characterized by insufficient angiogenesis.

Diseases characterized insufficient angiogenesis	Angiogenic mechanism	Therapeutic approach	References
Myocardial Ischemia	Imbalance in capillary-to-cardiomyocyte fiber ratio because of reduced VEGF levels	VEGF stimulates endothelial cells to proliferate and migrate, mobilizes endothelial progenitor cells	Ye et al., 2004 [63]
Myocardial Hypertrophy	Mismatch between the number of capillaries and cardiomyocytes per unit area	VEGF increases microvascular density, improves tissue perfusion, and glucose delivery	Friehs et al. 2004 [65]
Hypertension	Microvessel rarefaction (reduction in their density) because of impaired vasodilatation or angiogenesis	Angiogenic growth factors stimulate construction of new capillaries and recruitment of endothelial progenitor cells, which can be expected to decrease vascular resistance	Sica, 2006, Boudier 1999 [66,119]
Atherosclerosis	Impaired collateral vessel development	Both more complex and dependent on the stage of the disease process	Bertolino et al., 2005 [111]
Peripheral Arterial Disease and Critical Lower Limb Ischemia	Impaired growth of collateral vessels in response to obstructive arterial disease	Angiogenic growth factors stimulate endothelial cell migration and accelerate endothelial repair by enhancing post-injury re-endothelization	Collinson and Donnelly 2004, Makinen, 2003 [70,71]
Cerebral Ischemic Stroke	Correlation of capillary density (angiogenesis) and survival	Long-term benefits by stimulating angiogenesis may be important to help functional recovery and prevent the cognitive deterioration frequently seen in stroke patients	Slevin et al. 2006 [74]
Wound Healing	Angiogenic capillary sprouts invade the fibrin/ fibronectin-rich wound clot	In an in-vitro model of human sprout angiogenesis three-dimensional fibrin gel, simulating early wound clot supported capillary sprout formation	Tonneson et al. 2000 [75]
Ulcer Healing	Delayed healing because of production of angiogenesis inhibitors by pathogens (*H. pylori*)	Angiogenesis can enhance the microcirculation in the healing site	Jenkinson et al. 2002 [77]
Menorrhagia	Loss of normal Angiopoietin-1 (Ang-1) expression leads to inadequate vascular remodeling/maturation and excessive blood loss observed in menorrhagia. Fragility of SMC-poor vessels because of low Ang-1 production	Ang-1 promotes endothelial cell migration, sprouting, and survival in vitro; and in creases new vessel growth, branching, maturation, and integrity in vivo	Hewett et al. 2002 [79]
Diabetes Mellitus	Direct and indirect effects of hyperglycemia on endothelial cell proliferation, extracellular matrix and metalloproteases might be involved in the pathology of angiogenesis in many clinical manifestations of diabetes. Endothelial progenitor cell dysfunction contributes to the pathogenesis of vascular complications in type 1 diabetes	The emergence of the VEGF (and perhaps other growth factors) defective signaling paradigm in diabetes promises to enhance the understanding of various complications of diabetes and to redirect therapeutic efforts to search for intracellular drug targets	Carmeliet 2003, Simons, 2005 [3, 146]
Bone Disease	Impaired bone formation because of age-dependent decline of VEGF-driven angiogenesis; osteoporosis because of low VEGF; healing of fracture nonunion is impaired by insufficient angiogenesis	Improving angiogenesis may prevent trabecular bone loss in aging	Carmeliet 2003, Martinez et al. 2002 [3,84]
Emphysema	Alveolar EC apoptosis upon VEGF inhibition	Chronic treatment of rats with the VEGF receptor blocker SU5416 led to enlargement of the air spaces as well as induced alveolar septal cell apoptosis, indicative of emphysema. Thus, inhibition of apoptosis by VEGF receptor signaling may offer a new strategy for the treatment of emphysema	Carmeliet 2003, Kasahara et al., 2000 [3,86]

Table III (*Continued*).

Diseases characterized insufficient angiogenesis	Angiogenic mechanism	Therapeutic approach	References
Pre-eclampsia	EC dysfunction, resulting in organ failure, thrombosis and hypertension because of deprivation of VEGF by soluble Flt1	Decreased concentrations of circulating free PlGF and free VEGF may have implications for the pathogenesis of pregnancy-induced hypertension and pre-eclampsia	Levine et al., 2004 [88]
Hair growth	Perifollicular angiogenesis is correlated with upregulation of VEGF mRNA expression by follicular keratinocytes of the outer root sheath	Transgenic over expression of VEGF in outer root sheath keratinocytes of hair follicles-induced perifollicular vascularization, resulting in accelerated hair regrowth after depilation and increased size of hair follicles and hair shafts. Conversely, treatment with a neutralizing anti-VEGF antibody led to hair growth retardation and reduced hair follicle size	Yano et al., 2001 [89]

Table IV Diseases characterized by excessive angiogenesis.

Diseases characterized excessive angiogenesis	Angiogenic mechanism	Therapeutic approach	References
Arthritis	Angiogenesis is the key event in the formation and maintenance of the pannus in rheumatoid arthritis	Inhibition reduces progression of the arthritis, prevent delivery of nutrients to the inflammatory site, vessel regression, hence reversal of disease	Roccaro et al. 2005 [120]
Hemangiomas	Proliferating hemangiomas express high levels of proliferating cell nuclear antigen, type IV collagenase, VEGF and FGF-2		Takahashi et al. 1994 [95]
Psoriasis	Fundamental inflammatory response. Significant abnormalities of vascular morphology and angiogenic growth factors have been described in psoriasis	Severe combined immunodeficient (SCID) mice model, which triggers neovascularization and psoriatic plaque formation as well as rapid advances made by other investigators have shown that treating the psoriatic lesions by attacking the vasculature may be possible	Leong et al. 2005 [121]
Age-related macular degeneration	Vision loss because of choroidal neovascularization, VEGF, fibroblast growth factor 2, pigment epithelium-derived growth factor, angiopoietins serve as therapeutic targets.	With the elucidation of VEGF as a major causal factor in neovascular AMD, anti-VEGF agents may become foundation therapy, pegaptanib sodium, an anti-VEGF aptamer used in market	Ng and Adamis 2005 [97]
Kidney Disease	End-stage renal disease – loss of peritubular capillaries in interstitial cells producing ischemia because of loss of VEGF and increase in TSP-1	Increasing the expression of VEGF may be beneficial	Kang et al. 2001 [98]
	Autosomal-dominant polycystic kidney disease – Neovascularization may result in the formation of aneurysms responsible for the renal bleeding		Elsa et al. 2001 [99]
	Chronic kidney disease – deficient VEGF in the presence of enhanced endostatin		Futrakul et al. 2008 [100]
Inflammatory Bowel Disease Ulcerative colitis and Crohn's disease	Inflammation is favoured and maintained by a pathological angiogenesis. VEGF and b-FGF – higher in patients with IBD	Pharmacological inhibition of angiogenesis targeting VEGF has the potential to be a therapeutic strategy in IBD	Azzam 2007, Pousa et al. 2008 [101]
Cancer	Fundamental in tumor growth, progression and metastasis	Antagonism is highly selective, less prone to drug resistance. Several angiogenic mediators can be targeted	Eichhorn et al. 2007 [102]

sclerotic lesions remains a refractory problem. It has been argued that vascular smooth muscle cells-rich lesions are stable because of their high cellular content, whereas relatively acellular lesions, with a higher degree of calcification, fibrosis, and lipids, are more prone to fracture and rupture. Therefore, it could be argued that, by enriching the supply of nutrients to the plaque core, plaque neovascularization may increase plaque cellularity and thereby act as an underlying cause of plaque stabilization. The role of angiogenesis in atherosclerosis is likely to be both more complex and dependent on the stage of the disease process. In the early stages of human atherosclerosis, adventitial neovascularization may be necessary for significant intimal thickening but not for accumulation of cholesterol-laden macrophages in 'fatty streaks'. Most of the studies of atherosclerosis in neovascularization are performed on animals. Additional large animal studies of angiogenesis inhibitors and promoters are clearly required to clarify the role of neovascularization in models of vessel wall disease that mimic the human situation more closely. It remains to ask whether or not inhibition of angiogenesis could be a therapeutic target in atherosclerotic disease. The available evidence suggests that, although anti-angiogenic therapies may potentially have some effect on the growth of atherosclerotic and neointimal lesions, particularly in vein graft stenosis and restenosis after angioplasty, any benefit is likely to be nullified by the harmful effects of inhibiting endothelial function and regeneration [69].

5 Peripheral Arterial Disease

The physiological processes of angiogenesis, vasculogenesis, and arteriogenesis contribute to the growth of collateral vessels in response to obstructive arterial disease causing lower limb or myocardial ischemia, but in clinical practice the endogenous angiogenic response is often suboptimal or impaired, e.g. by factors such as aging, diabetes, or drug therapies. Therapeutic angiogenesis is an application of biotechnology to stimulate new vessel formation via local administration of pro-angiogenic growth factors (VEGF and bFGF) in the form of recombinant protein or gene therapy, or by implantation of endothelial progenitor cells that will synthesize multiple angiogenic cytokines [70,71].

6 Critical Lower Limb Ischemia

Patients with chronic critical limb ischemia who are not candidate for surgical or percutaneous revascularization have impending limb loss; those who benefit from successful revascularization suffer from high rate of recurrent symptoms or revision surgery or progressive amputations. In these patients, no medical treatment is considered effective for rest pain or ulcer healing. The discovery of the possibility of inducing sprouting of new vessels from pre-existing vasa (angiogenesis) or the in situ differentiation of endothelial cells from stem cell precursors (vasculogenesis) has open new lease on life [72]. Furthermore, with the growth factors being investigated as potential therapeutic agents, a combination of growth factors may be needed to provide the most effective treatment in view of the complex process of angiogenesis, which involves a cascade of events [73].

7 Cerebral Ischemic Stroke

The capillary density is found to be increased around infarcts in post-mortem brains of patients who had survived acute ischemic stroke for up to several weeks. The new blood vessels formed regular connections with intact microvessels within 1 week of ischemia. During the inflammatory phase of stroke, angiogenesis may be activated through release of polypeptide growth factors and cytokines originating from infiltrating macrophages, leukocytes, and damaged blood platelets. Specific upregulation of the angiogenic factors, including TGF-β (transforming growth factor-β), PDGF (platelet-derived growth factor), VEGF, and basic FGF (fibroblast growth factor)-2, occurs in the microvessels of patients in response to ischemic stroke. At least 20 small molecules and peptide growth factors are known to induce angiogenesis in ischemic stroke.

Pharmacological treatments stimulating angiogenesis and restoration of adequately perfused cerebral tissue may become an important therapeutic option in the near future. Multiple pre-clinical strategies have been employed for promoting angiogenesis in ischemic brain tissue. For example, human *VEGF* or *HGF* (hepatocyte growth factor) gene transfer, combination therapies of VEGF and angiopoietins, combination of VEGF with HIF prolyl hydroxylase inhibitors were found effective in promoting angiogenesis [74].

8 Wound Healing

During wound healing, angiogenic capillary sprouts invade the fibrin/fibronectin-rich wound clot and within a few days organize into a microvascular network throughout the granulation tissue. As collagen accumulates in the granulation tissue to produce scar, the density of blood vessels diminishes. A dynamic interaction occurs among endothelial cells,

angiogenic cytokines, such as FGF, VEGF, TGF-beta, angiopoietin, and mast cell tryptase, and the ECM environment. Wound ECM can regulate angiogenesis in part by modulating the integrin receptor expression like $\alpha_v\beta_3$, the integrin receptor for fibrin and fibronectin, which is expressed on the tips of angiogenic capillary sprouts invading the wound clot, and functional inhibitors of $\alpha_v\beta_3$ transiently inhibit granulation tissue formation. Wound angiogenesis also appears to be regulated by endothelial cell interaction with the specific three-dimensional ECM environment in the wound space. Understanding the molecular mechanisms that regulate wound angiogenesis, particularly how ECM modulates ECM receptor and angiogenic factor requirements, may provide new approaches for treating chronic wounds [75].

9 Ulcer Healing

Once a peptic ulcer has developed, angiogenesis plays a critical role in its healing by enhancing the microcirculation in the healing site. Helicobacter pylori infection significantly suppressed angiogenesis and delayed ulcer healing [76]. *H. pylori* can inhibit endothelial cell proliferation. *H. pylori induces* cytokine upregulation like IL-6, IL-8, and TNF-α, which could prove detrimental to ulcer healing through an inhibitory effect on angiogenesis [77]. *H. pylori* may also inhibit the expression of angiogenic growth factor receptors like VEGF and angiopoietin-1/-2 in vascular endothelial cells, which could further explain, in part, the delayed healing of gastric ulcer by *H. pylori* [78].

10 Menorrhagia

Angiogenesis is an essential component of endometrial repair and regeneration following menses. Perturbation of this process is associated with menorrhagia, a common gynecological disorder that results in excessive menstrual bleeding. The mechanisms controlling menstruation are regulated by local factors within the endometrium that include vasoregulators, angiogenic growth factors, and matrix metalloproteinases [79]. Peptide and nonpeptide angiogenic factors interact during endometrial renewal, including epidermal growth factor (EGF), transforming growth factors (e.g. TGF-β), platelet-derived endothelial growth factor/thymidine phosphorylase, tumor necrosis growth factors, and VEGF [80]. Disturbances of the normal processes of angiogenesis occurring in the endometrium during menstruation may result in menorrhagia. The normal pattern of Angiopoietin-1 expression is downregulated in the endometrium of women with menorrhagia [81].

11 Diabetes Mellitus

While diabetes management has largely focused on control of hyperglycemia, the presence of abnormalities of angiogenesis may cause or contribute to many of the clinical manifestations of diabetes-like vascular abnormalities of the retina, kidneys, diabetic neuropathy, impaired wound healing, increased risk of rejection of transplanted organs, and impaired formation of coronary collaterals. In patients with diabetes, the angiogenic response to chronic ischemia can be excessive in some of the target organs and insufficient in others, in the same individual [81]. Increased VEGF-mediated angiogenesis has been implicated in retinopathy and nephropathy, whereas there is an attenuated angiogenic response in wound healing and ulcers [82]. Diabetic patients have been reported to have a reduced number of circulating endothelial progenitor cells, with the extent of reduction directly proportional to plasma hemoglobin A1c levels. There are also reports of reduced VEGF and VEGF receptors expression in the myocardium of diabetic patients as well as increased production of an angiogenesis inhibitor angiostatin induced by hyperglycemia. The presence of advanced glycation end-products might well play an important role in suppressing arteriogenesis. It is also possible that intracellular signaling defects in diabetes are not limited to VEGF, but include other important arteriogenic growth factors such as FGFs, platelet-derived growth factors, hepatocyte growth factor, and placenta growth factor [83].

12 Bone Disease

Osteogenesis and angiogenesis occur in a coordinated manner in skeletal tissue, so that impaired angiogenesis is associated with decreased bone formation in aged subjects. Parathyroid hormone-related protein (PTHrP), a bone factor, which modulates osteoblastic cell growth and/or differentiation, stimulates VEGF, a potent angiogenic factor, in primary cultures of human osteoblastic (hOB) cells. Age-related bone loss in humans is associated with a decrease in the osteoblastic secretion of both PTHrP and VEGF in the knee, a predominantly trabecular bone [84].

13 Emphysema

Emphysema is defined as abnormal permanent enlargement of the airspaces distal to terminal bronchioles characterized by the disappearance of alveolar septa. It has been proposed that a reduction in the

blood supply of the small pre-capillary blood vessels might induce the disappearance of alveolar septa by Liebow [85]. The disappearance of lung tissue in emphysema may involve the progressive loss of capillary endothelial and epithelial cells through apoptosis. VEGF increases endothelial permeability and induces endothelial cell growth and thus required for the survival of the endothelial cells [86].

14 Pre-eclampsia

Abnormal indices of angiogenesis are evident in pregnancy-induced hypertension and pre-eclampsia, with higher levels of soluble fms-like tyrosine kinase 1 (sFIt-1) and lower levels of VEGF, increased levels of Ang-1 and Tie-2, but reduced Ang-2 compared to normal pregnancy [87]. Soluble fms-like tyrosine kinase 1 (sFlt-1), a circulating anti-angiogenic protein, is increased in the placenta and serum of women with pre-eclampsia, which acts by preventing the interaction of placental growth factor (PlGF) and VEGF with its endothelial receptors and thereby inducing endothelial dysfunction [88].

15 Hair growth

There is a significant increase in perifollicular vascularization during the growth phase (anagen) of the hair cycle, followed by regression of angiogenic blood vessels during the involution (catagen) and the resting (telogen) phase. VEGF is a major mediator of hair follicle growth and cycling and improves follicle vascularization promotes hair growth and increases hair follicle and hair size [89].

Diseases characterized by excessive angiogenesis

16 Arthritis

Rheumatoid arthritis (RA) is a chronic destructive musculo-skeletal disorder. The expansion of the synovial lining of joints in rheumatoid arthritis (RA) and the subsequent invasion by the pannus of underlying cartilage and bone necessitate an increase in the vascular supply to the synovium, to cope with the increased requirement for oxygen and nutrients. Angiogenesis occurs since the early stage of the disease and supports progression of the arthritis. Although many pro-angiogenic factors are expressed in the synovium in RA, the potent pro-angiogenic cytokine VEGF has been shown to a have a central involvement. Several studies have shown that targeting angiogenesis in animal models of arthritis ameliorates disease [90]. In addition, a limited number of human clinical trials gave promising results [91].

17 Hemangiomas

Hemangiomas are characterized by the proliferation of capillary endothelium with accumulation of mast cells, fibroblasts and macrophages. Hemangiomas are characterized by rapid neonatal growth (proliferating phase) for 6–10 months, which is followed by a very slow regression for the next 5–8 years (involuting phase) [92–94]. Several studies have shown that proliferating hemangiomas express high levels of proliferating cell nuclear antigen (PCNA, a marker for cells in the S phase), type IV collagenase, VEGF, and FGF-2 [95]. During the involuting phase of hemangiomas, expression of these angiogenic factors decreases.

18 Psoriasis

Psoriasis is a common chronic dermatosis and associated with an inflammatory arthritis. Angiogenesis appears to be a fundamental inflammatory response. Angiogenesis is an important component of acute and chronic psoriatic skin lesions as they are erythematosus and display a tendency to bleed after superficial removal of scale. The structural expansion of capillaries and distinctive activated phenotype of lesional endothelial cells play a central role in the pathogenesis of psoriatic plaques. It is likely that progress in understanding and treating psoriasis by attacking the vasculature will be part of our therapeutic strategy in the not so distant future [96].

19 Age-related macular degeneration

The pathogenesis of neovascular age-related macular degeneration (AMD) is complex, the underlying cause of vision loss being choroidal neovascularization (CNV). CNV may be initiated by a number of events, such as reduction in choriocapillaris blood flow, accumulation of lipid metabolic byproducts, oxidative stress, and alterations in Bruch's membrane. In response to metabolic distress, the retinal pigment epithelium and the retina produce factors, VEGF in particular, that act through a variety of mechanisms to cause CNV. VEGF serves as a 'master switch' for many ocular neovascular conditions through its promotion of endothelial cell proliferation and survival, vascular permeability, and ocular inflammation [97].

20 Kidney Disease

End-stage renal disease is characterized by progressive scarring of the glomeruli (glomerulosclerosis) and the interstitium (interstitial fibrosis). A remarkable loss of peritubular capillaries was observed in interstitial fibrosis in human disease as well as in

several experimental models, which result in impaired delivery of oxygen and nutrients to the tubules and interstitial cells, producing chronic ischemia. This was found to be correlated with loss of VEGF and increase in TSP-1 levels in kidney. Thus, impaired angiogenesis may have a crucial role in either causing or contributing to the development of end-stage renal disease [98].

Autosomal-dominant polycystic kidney disease (ADPKD) is a genetic disorder characterized by the formation of epithelial cell cysts, an increase in the ECM, and vascular alterations believed to be the result of compression by the cysts. There is a rich vascular network on the surface of the cysts, and thus, angiogenesis could be a factor in the progression of ADPKD. This process may be necessary for cyst cells to grow and may be responsible for increased vascular permeability facilitating fluid secretion into the cysts [99].

This process may be necessary for cyst cells to grow and may be responsible for increased vascular permeability facilitating fluid secretion into the cysts. A deficient VEGF in the presence of enhanced endostatin (anti-angiogenesis) implies a defective angiogenesis in chronic kidney disease, which may explain the progressive nature of renal microvascular disease observed in late stage of chronic kidney disease patients [100].

21 Inflammatory Bowel Disease (IBD)

There is considerable evidence of interrelation between the mechanisms of angiogenesis and the chronic inflammation of IBD. Both ulcerative colitis and Crohn's disease are recognized as perplexing and challenging clinical entities, in which several molecules and cell types are implicated. Recent molecular evidence proposes the intestinal microvascular remodeling or angiogenesis, as a phenomenon implicated in their pathogenesis. Intestinal damage is followed by a physiological angiogenesis, but the abnormal expression of pro- and anti-angiogenic molecules and the changes of vascular cell types could reflect a pathological vascular remodeling. Thus, the inflammation may be favoured and maintained by a pathological angiogenesis [101].

22 Cancer

The complex network of tumor blood microvessels guarantees adequate supply of tumor cells with nutrients and oxygen and provides efficient drainage of metabolites. The growth of a solid tumor is closely connected to the development of an intrinsic vascular network. In addition to primary tumor growth, metastatic tumor growth depends upon neovascularization in at least two steps: First, malignant cells must exit from a primary tumor into the blood circulation after the tumor becomes neovascularized. Second, after arrival at distant organs, metastatic cells must again induce angiogenesis for a tumor to expand to a detectable size [102]. The control of tumor angiogenesis depends on a net balance of several activators (angiogenic factors) and inhibitors (anti-angiogenic factors), which are secreted by both tumor cells and host infiltrating cells such as macrophages and fibroblasts. The development of new blood vessels in a tumor starts with the release of angiogenic factors, which bind to specific receptors of endothelial cells of pre-existing blood vessels to trigger the process of angiogenesis. During this process, endothelial cell adhesion molecules such as integrin $\alpha_v\beta_3$ and vascular adhesion molecule-1 help to connect new vessels with the pre-existing ones to produce the intratumoral vascular network [103].

There are more than 40 known endogenous inducers and inhibitors of angiogenesis to date. The best characterized angiogenic factor is VEGF, others include basic fibroblast growth factor, platelet-derived endothelial cell growth factor, angiogenin, angiopoietins as well as cyclo-oxygenase-2. Among the anti-angiogenic factors, thrombospondin-1 is considered an important inhibitor of tumor angiogenesis. Two other potent anti-angiogenic factors are angiostatin and endostatin play an important role in tumor dormancy [103].

Targeting the proliferating endothelial cells may have following theoretical advantages over cytotoxic chemotherapy: (i) They are not restricted to a certain histologic tumor entity, as all solid tumors depend on angiogenesis and the maintenance of functional microvasculature. The tumor microvasculature is well accessible to systemic treatment. (ii) In contrast to chemotherapy, no endothelial barrier has to be crossed by the therapeutic substances. (iii) Angiogenesis in adult organisms is only induced under certain physiologic conditions, i.e. during the reproductive ovarian cycle or wound healing. An antagonism of angiogenesis is therefore a highly selective therapy promising less serious side effects. The endothelial cell as a target is genetically stable and, therefore, suggested to be less prone to development of drug resistance [102].

CONCLUSIONS

Insight into the fundamental physiological mechanisms of blood vessel development and neoformation has led to the discovery of multiple angiogenic growth factors and inhibitors. A clear concept of the role of angiogenesis in cancer and other diseases has now emerged. The realization that various diseases including tumor growth require new blood vessels and the identification of chemical factors that mediate or inhibit angiogenesis have broadened our understanding of pathologic processes. Clinical applications of research on angiogenesis have taken three directions: the quantitation of angiogenesis for use in diagnosis and prognosis, the acceleration of angiogenesis during repair, and the inhibition of angiogenesis in various disorders. However, challenges still remain as to which angiogenic factor or combination of factors can be used to target the pathological states.

REFERENCES

1 Hirschi K.K., d'Amore P.A. Pericytes in the microvasculature. Cardiovasc. Res. (1996) **32** 687–698.
2 Liekens S., De Clercq E., Neyts J. Angiogenesis: regulators and clinical applications. Biochem. Pharmacol. (2001) **61** 253–270.
3 Carmeliet P. Angiogenesis in health and disease. Nat. Med. (2003) **9** 653–660.
4 Hyder S.M., Stancel G.M. Regulation of angiogenic growth factors in the female reproductive tract by estrogens and progestins. Mol. Endocrinol. (1999) **13** 806–811.
5 Conway E.M., Collen D., Carmeliet P. Molecular mechanisms of blood vessel growth. Cardiovasc. Res. (2001) **49** 507–521.
6 Polverini P.J. The pathophysiology of angiogenesis. Crit. Rev. Oral Biol. Med. (1995) **6** 230–247.
7 Prior B.M., Yang H.T., Terjung R.L. What makes vessels grow with exercise training? J. Appl. Physiol. (2004) **97** 1119–1128.
8 Fava R.A., Olsen N.J., Spencer-Green G. et al. Vascular permeability factor/endothelial growth factor (VPF/VEGF): accumulation and expression in human synovial fluids and rheumatoid synovial tissue. J. Exp. Med. (1994) **180** 341–346.
9 Koch A.E., ; Harlow L.A., Haines G.K. et al. Vascular endothelial growth factor. A cytokine modulating endothelial function in rheumatoid arthritis. J. Immunol. (1994) **152** 4149–4156.
10 Lee S.H., Wolf P.H., Escuredo R., Deutsch R., Jamieson S., Thistlethwaite P. Early expression of angiogenesis factors in acute myocardial ischemia and infarction. N. Engl. J. Med. (2000) **342** 626–633.
11 Cooke J.P., Losordo D.W. Nitric oxide and angiogenesis. Circulation (2002) **105** 2185–2191.
12 Gupta K., Zhang J. Angiogenesis: a curse or cure? Postgrad. Med. J. (2005) **81** 236–242.
13 Curran S., Murray G.I. Matrix metalloproteinases in tumour invasion and metastasis. J. Pathol. (1999) **189** 300–308.
14 Post S., Peeters W., Busser E. et al. Balance between angiopoietin-1 and angiopoietin-2 is in favor of angiopoietin-2 in atherosclerotic plaques with high microvessel density. J. Vasc. Res. (2008) **45** 244–250.
15 Oike Y., Yasunaga K., Suda T. Angiopoietin-related/angiopoietin-like proteins regulate angiogenesis. Int. J. Hematol. (2004) **80** 21–28.
16 Morisada T., Kubota Y., Urano T., Suda T., Oike Y. Angiopoietins and angiopoietin-like proteins in angiogenesis. Endothelium (2006) **13** 71–79.
17 Vallee B.L., Riordan J.F. Organogenesis and angiogenin. Cell. Mol. Life Sci. (1997) **53** 803–815.
18 Moghaddam A., Zhang H.T., Fan T.P.D. et al. Thymidine phosphorylase is angiogenic and promotes tumor growth. Proc. Natl Acad. Sci. USA (1995) **92** 998–1002.
19 Giatromanolaki A., Koukourakis M.I., Sivridis E. et al. Expression of hypoxia-inducible carbonic anhydrase-9 relates to angiogenic pathways and independently to poor outcome in non-small cell lung cancer. Cancer Res. (2001) **61** 7992–7998.
20 Woods J.M., Mogollon A., Amin M.A., Martinez R.J., Koch A.E. The role of COX-2 in angiogenesis and rheumatoid arthritis. Exp. Mol. Pathol. (2003) **74** 282–290.
21 Fosslien E. Molecular pathology of cyclooxygenase-2 in cancer-induced angiogenesis. Ann. Clin. Lab. Sci. (2001) **31** 325–348.
22 Curzio R., Oliver D., Agnese M. Endothelial cell integrins and COX-2: mediators and therapeutic targets of tumor angiogenesis. Rev. Cancer (2004) **1654** 51–67.
23 Blom I., van Dijk A., Wieten L. et al. In vitro evidence for differential involvement of CTGF, TGFbeta, and PDGF-BB in mesangial response to injury. Nephrol. Dial. Transplant. (2001) **16** 1139–1148.
24 Stratton R., Shiwen X., Martini G. et al. Iloprost suppresses connective tissue growth factor production in fibroblasts and in the skin of scleroderma patients. J. Clin. Invest. (2001) **108** 241–250.
25 Chen C.C., Chen N., Lau L.F. The angiogenic factors Cyr61 and CTGF induce adhesive signaling in primary human skin fibroblasts. J. Biol. Chem. (2001) **276** 10443–10452.
26 Shimo T., Kubota S., Kondo S. et al. Connective tissue growth factor as a major angiogenic agent that is induced by hypoxia in a human breast cancer cell line. Cancer Lett. (2001) **174** 57–64.
27 Distler J.W., Hirth A., Kurowska-Stolarska M., Gay R.E., Gay S., Distler O. Angiogenic and angiostatic factors in the molecular control of angiogenesis. Q. J. Nucl. Med. (2003) **47** 149–161.
28 Agrotis A., Kalinina N., Bobik A. Transforming growth factor-β, cell signaling and cardiovascular disorders. Curr. Vasc. Pharmacol. (2005) **3** 55–61.

29 Frank J., Born K., Barker J.H., Marzi I. In vivo effect of tumor necrosis factor alpha on wound angiogenesis and epithelialization. Eur. J. Trauma (2003) **29** 208–219.
30 Nabors L.B., Suswam E., Huang Y., Yang X., Johnson M.J., King P.H. Tumor necrosis factor α induces angiogenic factor up-regulation in malignant glioma cells. Cancer Res. (2003) **63** 4181–4187.
31 Gardiner T.A., Gibson D.S., de Gooyer T.E., de la Cruz V.F., McDonald D.M., Stitt A.W. Inhibition of tumor necrosis factor-α improves physiological angiogenesis and reduces pathological neovascularization in ischemic retinopathy. Am. J. Pathol. (2005) **166** 637–644.
32 Pucci A., Martino S., Celeste A. et al. Angiogenesis, tumor necrosis factor-α and procoagulant factors in coronary artery giant aneurysm of a fatal infantile Kawasaki disease. Cardiovasc. Pathol. (2008) **17** 186–189.
33 Strieter R.M., Belperio J.A., Keane M.P. CXC chemokines in angiogenesis related to pulmonary fibrosis. Chest (2002) **122** 298S–301S.
34 Strieter R.M., Burdick M.D., Gomperts B.N., Belperio J.A., Keane M.P. CXC chemokines in angiogenesis. Cytokine Growth Factor Rev. (2005) **16** 593–609.
35 Salven P., Hattori K., Heissig B., Rafii S. Interleukin-1α promotes angiogenesis in vivo via VEGFR-2 pathway by inducing inflammatory cell VEGF synthesis and secretion. FASEB J. (2002) **16** 1471–1473.
36 Heidemann J., Ogawa H., Dwinell M.B. et al. Angiogenic effects of interleukin 8 (CXCL8) in human intestinal microvascular endothelial cells are mediated by CXCR2. J. Biol. Chem. (2003) **278** 8508–8515.
37 McClintock J.Y., Wagner E.M. Role of IL-6 in systemic angiogenesis of the lung. J. Appl. Physiol. (2005) **99** 861–866.
38 Rabascio C., Muratori E., Mancuso P. et al. Assessing tumor angiogenesis: increased circulating VE-cadherin RNA in patients with cancer indicates viability of circulating endothelial cells. Cancer Res. (2004) **64** 4373–4377.
39 Martin T.A., Watkins G., Lane J., Jiang W.G. Assessing microvessels and angiogenesis in human breast cancer, using VE cadherin. Histopathology (2005) **46** 422–430.
40 Wang Y., Zhen Y., Shi Y. et al. Vitamin K epoxide reductase: a protein involved in angiogenesis. Mol. Cancer Res. (2005) **3** 317–323.
41 Saito A., Sugawara A., Uruno A. et al. All-*trans* retinoic acid induces *in vitro* angiogenesis via retinoic acid receptor: possible involvement of paracrine effects of endogenous vascular endothelial growth factor signaling. Endocrinology (2007) **148** 1412–1423.
42 Klagsbrun M., Moses M.A. Molecular angiogenesis. Chem. Biol. (1999) **6** 217–224.
43 Folkman J. Fundamental concepts of the angiogenic process. Curr. Mol. Med. (2003) **3** 643–651.
44 Ying S., Jiah-si Z. Canstatin, a endogenous inhibitor of angiogenesis and tumor growth. Chin. J. Cancer Res. (2004) **16** 229–234.
45 Lobov I.B., Renard R.A., Papadopoulos N. et al. Delta-like ligand 4 (Dll4) is induced by VEGF as a negative regulator of angiogenic sprouting. Proc. Natl Acad. Sci. USA (2007) **104** 3219–3224.
46 Hayami T., Funaki H., Yaoeda K. et al. Expression of the cartilage derived anti-angiogenic factor chondromodulin-I decreases in the early stage of experimental osteoarthritis. J. Rheumatol. (2003) **10** 2207–2217.
47 Sasisekharan R., Moses M.A., Nugent M.A., Cooney C.L., Langer R. Heparinase inhibits neovascularization. Proc. Natl Acad. Sci. USA (1994) **91** 1524–1528.
48 Lee P.L.Q., Holme K.R., Symes J.F. Heparinase enhances collateral vessel development in the ischemic limb. Int. Surg. (2002) **87** 260–268.
49 Ji W.R., Barrientos L.G., Llinas M. et al. Selective inhibition by kringle 5 of human plasminogen on endothelial cell migration, an important process in angiogenesis. Biochem. Biophys. Res. Commun. (1998) **247** 414–419.
50 Zhou Y., Zheng Q., Gao J., Gu J. High level expression of kringle 5 fragment of plasminogen in *Pichiapastoris*. Biotechnol. Lett. (2005) **27** 167–171.
51 Zhang L., Chen J., Ke Y., Mansel R.E., Jiang W.G. Expression of pigment epithelial derived factor is reduced in non-small cell lung cancer and is linked to clinical outcome. Int. J. Mol. Med. (2006) **17** 937–944.
52 Filleur S., Volz K., Nelius T. et al. Two functional epitopes of pigment epithelial–derived factor block angiogenesis and induce differentiation in prostate cancer. Cancer Res. (2005) **65** 5144–5152.
53 Majewski S., Marczak M., Szmurlo A., Jablonska S., Bollag W. Retinoids, Interferon α, 1,25-dihydroxyvitamin D3, their combination inhibit angiogenesis induced by non-HPV-harboring tumor cell lines. RARα mediates the antiangiogenic effect of retinoids. Cancer Lett. (1995) **89** 117–124.
54 Lachgar S., Charvéron M., Gall Y., Bonafé J.L. Inhibitory effects of retinoids on vascular endothelial growth factor production by cultured human skin keratinocytes. Dermatology (1999) **199** 25–27.
55 Beatrice K.E., James B.H., Bozena A.A. et al. Troponin I peptide (Glu94-Leul23), a cartilage-derived angiogenesis inhibitor: in vitro and in vivo effects on human endothelial cells and on pancreatic cancer. J. Gastrointest. Surg. (2003) **7** 961–969.
56 Schwartz J.D., Sung M., Schwartz M. et al. Thalidomide in advanced hepatocellular carcinoma with optional low-dose interferon-α2a upon progression. Oncologist (2005) **10** 718–727.
57 Lindner D.J. Interferons as antiangiogenic agents. Curr. Oncol. Rep. (2002) **4** 510–514.
58 Volpert O.V., Fong T., Koch A.E. et al. Inhibition of angiogenesis by interleukin 4. J. Exp. Med. (1998) **188** 1039–1046.
59 Akhtar N., Padilla M.L., Dicjerson E.B. et al. Interleukin-12 inhibits tumor growth in a novel angiogenesis canine hemangiosarcoma xenograft model. Neoplasia (2004) **6** 106–116.
60 Siddiqui F., Ehrhart E.J., Charles B. et al. Anti-angiogenic effects of interleukin-12 delivered by a novel hyperthermia induced gene construct. Int. J. Hyperthermia (2006) **22** 587–606.

61 Harjai K.J., Chowdhury P., Grines C.L. Therapeutic angiogenesis: a fantastic new adventure. J. Interv. Cardiol. (2002) **15** 223–229.
62 Rosingberg A., Khan T.A., Sellke F.W., Laham R.J. Therapeutic angiogenesis for myocardial ischemia. Expert Rev. Cardiovasc. Ther. (2004) **2** 271–283.
63 Ye L., Haider H.K., Jiang S.J., Sim E.K. Therapeutic angiogenesis using vascular endothelial growth factor. Asian Cardiovasc. Thorac. Ann. (2004) **12** 173–181.
64 Syed I.S., Sandborn T.A., Rosengart T.K. Therapeutic angiogenesis: a biologic bypass. Cardiology (2004) **101** 131–143.
65 Friehs I., Moran A.M., Stamm C. et al. Promoting angiogenesis protects severely hypertrophied hearts from ischemic injury. Ann. Thorac. Surg. (2004) **77** 2004–2010.
66 Sica D.A. Angiogenesis inhibitors and hypertension: an emerging issue. J. Clin. Oncol. (2006) **24** 1329–1331.
67 Sane D., Anton L., Brosnihan K. Angiogenic growth factors and hypertension. Angiogenesis (2004) **7** 193–201.
68 Brizzi M.F., Formato L., Bonamini R. The molecular mechanisms of angiogenesis: a new approach to cardiovascular diseases. Ital. Heart. J. (2001) **2** 81–92.
69 Khurana R., Simons M., Martin J.F., Zachary I.C. Role of angiogenesis in cardiovascular disease a critical appraisal. Circulation (2005) **112** 1813–1824.
70 Collinson D.J., Donnelly R. Therapeutic angiogenesis in peripherial arterial disease: can biotechnology produce an effective collateral circulation? Eur. J. Vasc. Endovasc. Surg. (2004) **28** 9–23.
71 Makinen K. Angiogenesis – a new goal in peripheral artery occlusive disease therapy. Acta Chir. Belg. (2003) **103** 470–474.
72 Di Stefano R., Limbruno U., Barone D., Balbarini A. Therapeutic angiogenesis of critical lower limb ischemia. Review of the literature and prospects of research on stem cells. Ital. Heart. J. Suppl. (2004) **1**(Suppl) 1–13.
73 Kok Ho T., Rajkumar V., Black D.C., Abrahan D., Baker D. Critical limb ischemia classification and therapeutic angiogenesis. Int. J. Angiol. (2005) **14** 49–59.
74 Slevin M., Kumar P., Gaffney J., Kumar S., Jersy K. Can angiogenesis be exploited to improve stroke outcome? Mechanisms and therapeutic potential. Clin. Sci. (2006) **111** 171–183.
75 Tonnesen M.G., Feng X., Clark R.A. Angiogenesis in wound healing. J. Investig. Dermatol. Symp. Proc. (2000) **5** 40–46.
76 Gunawan E., Tsuji S., Tsuji M. et al. Influences of Helicobacter pylori on gastric angiogenesis and ulcer healing in mice. J. Gastroenterol. Hepatol. (2002) **17** 960–965.
77 Jenkinson L., Bardhan K.D., Atherton J., Kalia N. Helicobacter pylori prevents proliferative stage of angiogenesis in vitro: role of cytokines. Dig. Dis. Sci. (2002) **47** 1857–1862.
78 Kim J.S., Kim J.M., Jung H.C., Song I.S. Helicobacter pylori down-regulates the receptors of vascular endothelial growth factor and angiopoietin in vascular endothelial cells: implications in the impairment of gastric ulcer healing. Dig. Dis. Sci. (2004) **49** 778–786.
79 Hewett P., Nijjar S., Shams M., Morgan S., Gupta J., Ahmed A. Down-regulation of angiopoietin-1 expression in menorrhagia. Am. J. Pathol. (2002) **160** 773–780.
80 Smith S. Angiogenesis, vascular endothelial growth factor and the endometrium. Hum. Reprod. Update (1998) **4** 509–519.
81 Larger E. Hyperglycemia and angiogenesis. Med. Sci. (Paris) (2003) **19** 840–846.
82 Hazarika S., Dokun A.O., Li Y., Popel A.S., Kontos C.D., Annex B.H. Impaired angiogenesis after hind limb ischemia in type 2 diabetes mellitus. differential regulation of vascular endothelial growth factor receptor 1 and soluble vascular endothelial growth factor receptor 1. Circ. Res. (2007) **101** 948.
83 Simons M. Angiogenesis, arteriogenesis, and diabetes paradigm reassessed? J. Am. Coll. Cardiol. (2005) **46** 835–837.
84 Martinez P., Esbrit P., Rodrigo A., Alvarez-Arroyo M.V., Martinez M.E. Age-related changes in parathyroid hormone-related protein and vascular endothelial growth factor in human osteoblastic cells. Osteoporos. Int. (2002) **13** 874–881.
85 Liebow A.A. Pulmonary emphysema with special emphasis to vascular changes. Am. Rev. Respir. Dis. (1959) **80** 67–93.
86 Kasahara Y., Tuder R.M., Taraseviciene-Stewart L. et al. Inhibition of VEGF receptors causes lung cell apoptosis and emphysema. J. Clin. Invest. (2000) **106** 1311–1319.
87 Nadar S.K., Karalis L., Al Yemeni E., Blann A.D., Lip G.Y. Plasma markers of angiogenesis in pregnancy induced hypertension. Thromb. Haemost. (2005) **94** 1071–1076.
88 Levine R.J., Maynard S.E., Qian C. et al. Circulating angiogenic factors and the risk of preeclampsia. N. Engl. J. Med. (2004) **350** 672–683.
89 Yano K., Brown L.F., Detmar M. Control of hair growth and follicle size by VEGF-mediated angiogenesis. J. Clin. Invest. (2001) **107** 409–417.
90 Paleolog E.M. Angiogenesis in rheumatoid arthritis. Arthritis Res. (2002) **4**(Suppl 3) S81–S90.
91 Szekanecz Z., Gáspár L., Koch A.E. Angiogenesis in rheumatoid arthritis. Front. Biosci. (2005) **10** 1739–1753.
92 Drolet B.A., Esterly N.B., Frieden I.J. Hemangiomas in children. N. Engl. J. Med. (1999) **341** 173–181.
93 Mueller B.U., Mulliken J.B. The infant with a vascular tumor. Semin. Perinatol. (1999) **23** 332–340.
94 Powell J. Update on hemangiomas and vascular malformations. Curr. Opin. Pediatr. (1999) **11** 457–463.
95 Takahashi K., Mulliken J.B., Kozakewich H.P., Rogers R.A., Folkman J., Ezekowitz R.A. Cellular markers that distinguish the phases of hemangioma during infancy and childhood. J. Clin. Invest. (1994) **93** 2357–2364.
96 Nickoloff B.J. Characterization of lymphocyte-dependent angiogenesis using a SCID mouse: human skin model of psoriasis. J. Investig. Dermatol. Symp. Proc. (2000) **5** 67–73.
97 Ng E.W.M., Adamis A.P. Targeting angiogenesis, the underlying disorder in neovascular age-related macular degeneration. Can. J. Ophthalmol. (2005) **40** 352–368.
98 Kang D.H., Joly A.H., Oh S.W. et al. Impaired angiogenesis in the remnant kidney model: I. potential role of vascular endothelial growth factor and thrombospondin-1. J. Am. Soc. Nephrol. (2001) **12** 1434–1447.

99 Elsa B.R., Keith H., Srinivasan R. Angiogenesis in autosomal-dominant polycystic kidney disease. Kidney Int. (2001) **60** 37–45.

100 Futrakul N., Butthep P., Laohareungpanya N., Chaisuriya P., Ratanabanangkoon K. A defective angiogenesis in chronic kidney disease. Ren. Fail. (2008) **30** 215–217.

101 Pousa I.D., Mate J., Gisbert J.P. Angiogenesis in inflammatory bowel disease. Eur. J. Clin. Invest. (2008) **38** 73–81.

102 Eichhorn M.E., Kleespies A., Angele M.K., Jauch K.W., Bruns C.J. Angiogenesis in cancer: molecular mechanisms, clinical impact. Langenbecks Arch. Surg. (2007) **392** 371–379.

103 Pang R.W.C., Poon R.T.P. Clinical implications of angiogenesis in cancers. Vasc. Health Risk Manag. (2006) **2** 97–108.

104 Matsunaga T., Weihrauch D.W., Moniz M.C. et al. Angiostatin inhibits coronary angiogenesis during impaired production of nitric oxide. Circulation (2002) **105** 2133.

105 Mignatti P., Rifkin D.B. Plasminogen activators and matrix metalloproteinases in angiogenesis. Enzyme Protein (1996) **49** 117–137.

106 Thurston G., Suri C., Smith K. et al. Leakage- resistant blood vessels in mice transgenically overexpressing angiopoietin-1. Science (1999) **286** 2511–2514.

107 Wiedlocha A. Following angiogenin during angiogenesis: a journey from the cell surface to the nucleolus. Arch. Immunol. Ther. Exp. (Warsz) (1999) **47** 299–305.

108 Sengupta S., Sellers L.A., Matheson H.B., Fan T.P.D. Thymidine phosphorylase induces angiogenesis *in vivo* and *in vitro*: an evaluation of possible mechanisms. Br. J. Pharmacol. (2003) **139** 219–231.

109 Kireeva M.L., Latinkic B.V., Kolesnikova T.V. et al. Cyr61 and Fisp12 are both ECM-associated signaling molecules: activities, metabolism, and localization during development. Exp. Cell Res. (1997) **233** 63–77.

110 Holmes A., Abraham D., Sa S., Shiwen X., Black C., Leask A. CTGF and SMADs, Maintenance of scleroderma phenotype is independent of SMAD signaling. J. Biol. Chem. (2001) **276** 10594–10601.

111 Bertolino P., Deckers M., Lebrin F., Dijke P. Transforming growth factor β signal transduction in angiogenesis and vascular disorders. Chest (2005) **128** 585S–590S.

112 Bussolino F., Wang J.M., Turrini F. et al. Stimulation of the Na+/H+ exchanger in human endothelial cells activated by granulocyte and granulocyte macrophage colony stimulating factor. Evidence for a role in proliferation and migration. J. Biol. Chem. (1989) **264** 18284–18287.

113 Hockel M., Jung W., Vaupel P., Rabes H., Khaledpour C., Wissler J.H. Purified monocyte derived angiogenic substance (angiotropin) induces controlled angiogenesis associated with regulated tissue proliferation in rabbit skin. J. Clin. Invest. (1988) **82** 1075–1090.

114 Oh J.S., Kucab J.E., Bushel P.R. et al. Insulin-like growth factor 1 inscribes a gene expression profile for angiogenic factor and cancer progression in breast epithelial cells. Neoplasia (2002) **4** 204–217.

115 Matsumoto K., Nakamura T. Emerging multipotent aspects of hepaocyte growth factor. J. Biochem. (Tokyo) (1996) **119** 591–600.

116 Ashley R.A., Dubuque S.H., Dvorak B., Woodward S.S., Williams S.K., Kling P.J. Erythropoietin stimulates vasculogenesis in neonatal rat mesenteric microvascular endothelial cells. Pediatr. Res. (2002) **51** 472–478.

117 Yasuda Y., Fujita Y., Masuda S. et al. Erythropoietin is involved in growth and angiogenesis in malignant tumors of female reproductive organs. Carcinogenesis (2002) **23** 1797–1805.

118 Feldman E., Weinreich D., Carroll N. et al. Interferon γ–inducible protein 10 selectively inhibits proliferation and induces apoptosis in endothelial cells. Ann. Surg. Oncol. (2006) **13** 125–133.

119 Boudier H.A. Arteriolar and capillary remodelling in hypertension. Drugs (1999) **58** 37–40.

120 Roccaro A.M., Russo F., Cirulli T., Di Pietro G., Vacca A., Dammacco F. Antiangiogenesis for rheumatoid arthritis. Curr. Drug. Targets Inflamm. Allergy (2005) **4** 27–30.

121 Leong T.T., Fearon U., Veale D.J. Angiogenesis in psoriasis and psoriatic arthritis: clues to disease pathogenesis. Curr. Rheumatol. Rep. (2005) **7** 325–329.