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## Angiogenesis in hematologic malignancies

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**Abstract** Angiogenesis defined as the blood vessel generation from preexisting blood vessels was found to play an important role in the progression of solid tumors. In addition, bone marrow-derived endothelial precursor cells may contribute to tumor angiogenesis. Recently angiogenesis induction was described in several hematologic neoplasms as leukemia, lymphoma, myelodysplastic syndrome and multiple myeloma (MM). Clinical angiogenesis research also termed as angiodiagnosis has established the prognostic relevance of markers of angiogenesis e.g., microvessel density and circulating levels of angiogenic peptides. Development of antiangiogenic treatment for hematologic neoplasms has recently been sparked by the success of Thalidomide (Thal) which has antiangiogenic properties in MM. Antiangiogenic treatment strategies are now being tested in clinical trials on several types of hematologic neoplasms.

**Keywords** Angiogenesis · Vasculogenesis · Leukemia · Lymphoma · Multiple myeloma

### Introduction

Blood vessels are critical for maintaining cellular homeostasis of virtually all cells in the human body and therefore all cells must reside within 100  $\mu\text{m}$  of a capillary [26, 41, 42]. The development of the vascular tree starts early in embryogenesis, involving development of endothelial cells from mesenchymal precursor cells, finally leading to the formation of the primitive vascular plexus [104]. Recruitment of other mesenchymal cells such as smooth muscle cells and fibroblasts subsequently stabilizes the early vascular network which is also expanded by a process called angiogenesis. Angiogenesis is the generation of new capillaries from preexisting

blood vessels e.g., by sprouting or by intussusception [104, 124]. Angiogenesis is tightly regulated in the adult organism and is only induced during the female reproductive cycle, tissue repair, and wound healing [37, 41, 42]. Pioneered by the work of J. Folkman it was recognized that angiogenesis plays an important role in tumor development, progression, and metastasis [41, 42, 53]. General principles of angiogenesis have been recognized as being organized into three stages including an initiation phase, a proliferative/invasive phase and a differentiation/maturation phase [22]. Research involved in deciphering the molecular and cellular component of angiogenesis also identified an immense heterogeneity between physiologic and tumor angiogenesis as well as between angiogenesis in different tumor entities, different stages of tumor progression, and tumor development in different organs [12, 14, 17, 26, 37, 104].

Several molecules, including a number of angiogenesis inhibitors, seem to be predominantly involved in tumor angiogenesis and – in contrast to physiologic angiogenesis – do not show a coordinate expression during the angiogenesis process [26]. Tumor vessels often lack functional perivascular cells. The tumor blood vessel wall may be a mosaic of tumor cells and endothelial cells [26].

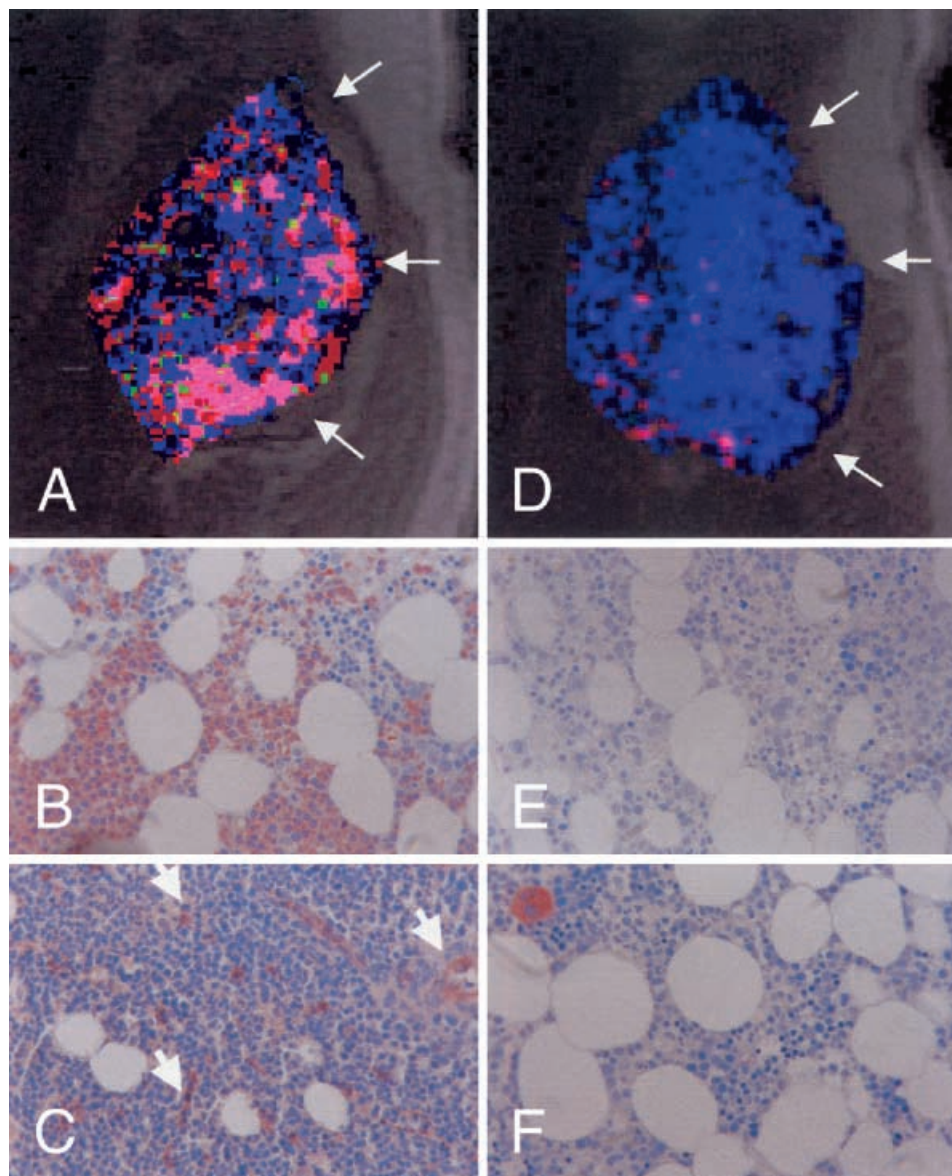
This review focuses on the current knowledge of angiogenesis and vasculogenesis in hematologic oncologic diseases. As angiogenesis in solid tumors has been studied much more extensively in clinically studies as well as in experimental work the review will refer to the results obtained in solid tumors and will try to link and compare the knowledge on angiogenesis in solid tumors with the angiogenic process in hematologic diseases.

### Evidence for angiogenesis in hematologic malignancies

Bone marrow and lymphatic organs of the body (e.g., lymph nodes, spleen) are the predominant sites for tumorigenesis in most hematologic oncologic diseases.

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**Fig. 1a–f** Comparison of dMRI maps and corresponding bone marrow biopsies in two patients with MM. **a, d** Color-coded parameter images superimposed onto the conventional STRF-MRI images of the pelvis in the area of spina iliaca superior posterior (*arrows* indicating iliacal crest) for two patients (patient 1: **a–c**, patient 2: **d–f**). **b, e** Histologic sections from bone marrow biopsies stained with anti-light chain antibodies showing the malignant plasma cell population in patient 1 (**b**) and lack of plasma cells in patient 2 (**e**). Serial sections stained with anti-factor VIII antibodies identified numerous blood vessels for patient 1 (**c**, *arrows* indicate selected blood vessels) and a lack of blood vessels for patient 2 (**f**, megakaryocytes stained as positive control, upper left corner) (T.M. Moehler et al., 2001 [82], with the permission of the publisher)



As leukemias and other hematologic neoplasms do not develop as compact tumor mass the necessity for angiogenesis was not as readily apparent as for solid tumors. In addition several mechanisms are under investigation which show how some tumors might circumvent the need for angiogenesis, at least at certain stages of tumorigenesis. Pezella et al. have shown that lung carcinomas can grow in the alveolar space exploiting the existing alveolar blood vessels rather than inducing angiogenesis [95]. This process was later described as cooption [26, 61, 124]. Interestingly, the coopted blood vessels may regress leading to an avascular partially necrotic tumor that subsequently induces the angiogenic process [124]. It was also proposed that in aggressive melanomas tumor cells may generate vessel-like channels permitting tumor perfusion without a vascular network. Several open questions are associated with this model, in particular how the proposed vascular channels are connected to

the vascular network [44, 77, 79]. All these data and considerations make it conceivable that there might be certain forms or developmental stages of leukemia or lymphomas that will progress independently of angiogenesis. Nevertheless several recent studies have provided evidence for angiogenesis induction in various hematologic oncologic diseases.

Knock-out experiments in mice suggest that there are three families of growth factors and their receptors that are functionally interconnected and play a central role in angiogenesis: VEGFs and VEGF receptors, angiopoietins and Tie2 receptors, ephrins, and Eph receptors [26, 108, 124].

In the case of VEGF even a single allele in VEGF knock-out mice led to embryonic lethality [104]. VEGF is also a potent inducer of vascular permeability and was therefore initially termed as the vascular permeability factor [93, 104]. In contrast to VEGF knock-out mice

**Table 1** Clinical studies indicative of angiogenesis induction in hematologic neoplasms and preneoplastic states (*CLL* chronic lymphatic leukemia, *IH* immunohistochemistry, *PL* concentration of angiogenic cytokines in peripheral blood and/or bone marrow, *RP* mRNA and protein expression of tumor cells, *dMRI* contrast-

enhanced dynamic magnetic resonance imaging, *MVD* microvessel density, *AILD* angioimmunoblastic lymphadenopathy with dysproteinemia). *EFS* event free survival; *OAS* overall survival; *MDS* myelodysplastic syndrome

Entity	Method indicating angiogenesis induction	Reference <sup>a</sup>	Angiogenesis parameter correlating with clinical data	Clinical parameter	Reference
<i>Acute leukemias</i>					
Acute myeloid leukemia	IH, RP	[1, 2, 39, 63, 92]	Intracellular VEGF in AML blasts	OAS	[1]
Acute lymphatic leukemia	IH	[94]			
<i>Non-Hodgkin lymphomas</i>					
Multiple myeloma	IH, PL, RP, dMRI	[32, 35, 82, 99, 102]	Bone marrow MVD dMRI amplitude <i>A</i>	EFS, OAS Major osteolytic bone involvement	[85, 99] [82]
Low/high-grade lymphomas	IH, PL, RP	[43, 97, 103]	PL-VEGF, PL-bFGF Bone marrow MVD	OAS NHL grading	[106] [103]
CLL	IH, RP	[4, 28, 69]	PL-VEGF	Risk of progression	[84]
AILD T cell lymphoma	IH	[43]			
<i>Hodgkin's lymphoma</i>	IH	[43]			
<i>Myelodysplastic syndrome</i>	IH	[96]	IH	MDS stage	[96]

<sup>a</sup> Examples of references

engineered to lack angiopoietin 1 (Ang1) and Tie2 developed a rather normal vascular plexus but failed to undergo normal vessel remodeling [26]. These and additional studies demonstrated that binding angiopoietin 1 to the Tie2 receptor expressed on endothelial cells promoted vessel maturation and development of mature blood vessels during the development of the vascular system.

Mouse embryos lacking ephrinB2 and its receptor tyrosine kinase Eph4 suffer fatal defects in early angiogenic remodelling that are reminiscent of those lacking Ang1 or Tie2. Importantly, ephrinB2 and EphB4 display remarkably reciprocal distribution patterns during vascular development, with ephrinB2 marking the endothelium of arterial vessels while EphB4 marks the endothelium of venous vessels. Therefore it is now believed that ephrinB2 and EphB4 play a important role in the development of the distinct characteristics of the venous and arterial blood vessels [124].

In cases of vessel cooption by tumor cells, host vessels start to express angiopoietin 2 which antagonizes the binding of Ang1 to the Tie2 receptor subsequently leading to vessel "destabilization" and promoting the proangiogenic effect of VEGF. The endothelium of new vessels in tumors strongly reexpresses ephrinB2.

According to the widely accepted angiogenic switch hypothesis the induction of angiogenesis and subsequent tumor progression is dependent on the balance of angiogenesis activators or inhibitors in the tumor microenvironment [52, 53]. In addition to the cytokines and their receptors discussed above a multitude of additional angiogenesis activators and inhibitors have been identified. Important activators of tumor angiogenesis are bFGF, epidermal growth factor, granulocyte colony stimulating

factor, interleukin-1, IL-6, IL-8, platelet-derived growth factor and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) [41, 42, 44, 117]. Of these VEGF and bFGF are particularly strong inducers of angiogenesis [111]. Inhibitors of VEGF or the VEGF signal pathway display in experimental models prominent antitumor effects in the presence of other angiogenesis activators [28, 68, 111, 117].

Immunohistochemistry using anti CD31 is still considered the gold standard in the detection of angiogenesis but a considerable sampling error has to be taken into account and the functional status (e.g., permeability) of the blood vessels cannot be determined [76, 122].

Other techniques such as contrast-enhanced dynamic magnetic resonance imaging (dMRI) do not allow a direct quantification blood vessel density but provide information on the functional status of the blood vessels e.g., permeability [20, 21, 48, 57, 58, 59]. Examples of these two techniques are presented in Fig. 1 showing two patients with MM [82]. In addition several other techniques are described that may reflect at least part of the angiogenic process in vivo (e.g., investigation of circulating levels of angiogenic peptides and endothelial specific receptor tyrosine kinases). Due to the limitations of each marker of angiogenesis results should be interpreted cautiously to avoid pitfalls, some of which are described in this review [76].

Table 1 summarizes clinical studies that are indicative of angiogenesis induction in hematologic neoplasms and preneoplastic states.

Synthesis of VEGF and other angiogenic factors such as bFGF and HGF has been demonstrated for leukemia cells, non-Hodgkin-lymphoma (NHL), and myeloma cells (Table 1) [1, 10, 32, 43]. Angiogenic peptides may also be produced by other cells e.g., fibroblasts in the

stroma and immune cells [76, 108]. The bone marrow osteoclasts are a rich source of angiogenic factors which are activated in multiple myeloma [67, 87]. Furthermore, macrophage and mast cell density were found to be positively correlated with angiogenesis in B-cell non-Hodgkin-lymphoma suggesting the proangiogenic role of these cells since they release factors such as tryptase and angiogenic peptides (Fig. 2) [121].

The detection of angiogenic molecules in the clinical situation should help to determine whether angiogenesis activators are present as a prerequisite of the angiogenic cascade. This appears most likely in those cases where angiogenic peptides can be detected in the tumor compartment. In MM bone marrow levels of the angiogenic peptides VEGF are significantly elevated in comparison to VEGF levels in peripheral blood, while both peripheral blood and bone marrow levels are increased in comparison to normal controls [35, 110]. An increased expression of angiogenic peptides was also shown in other hematologic neoplasms such as NHL and chronic lymphatic leukemia (CLL) [4, 43]. The results of these measurements in correlation with clinical parameters are summarized in Table 1 and discussed in the next section. However, the detection of the angiogenic peptides in clinical samples gives no information about the cellular source of these molecules and certainly does not prove that there is ongoing angiogenesis in the compartment under investigation. For example, thrombocytes and mononuclear cells are a rich source of VEGF which is released during the coagulation process [5, 108, 121].

Multiple anti-angiogenic molecules have been identified in recent years. These include cytokines such as IFN-alpha and gamma as well as several peptides generated by proteolytic cleavage of the basement membrane, and proteins of the fibrinolytic and clotting pathway (e.g., angiostatin, endostatin, maspin, vasculostatin) [31, 91, 105, 117, 126]. Thus, endostatin could be detected in NHL [15]. Recently, a fragment of matrix metalloproteinase 2 (MMP-2) containing the substrate binding site was also found to be anti-angiogenic [24]. It has been elegantly shown in several experimental models that downregulation of a single inhibitor e.g., thrombospondin in the presence of angiogenesis activators can induce angiogenesis and tumor progression [31].

Induction of angiogenesis does not only occur in neoplastic hematologic diseases but also to a significant extent in myelodysplastic syndrome (MDS), a preneoplastic disease. In the case of MDS microvessel density is significantly increased over normal controls during progression of the stages of MDS (according to FAB classification) showing highest microvessel counts in chronic myelomonocytic leukemia (CMML) and secondary AML, and the lowest (but still significantly higher than in controls) in refractory anemia (RA) [96]. This investigation shows evidence that angiogenesis induction might be an event in tumorigenesis of hematologic disease similar to the angiogenic switch proposed for solid tumors [52, 53, 101, 102, 103]. A direct link between chromosomal aberrations and angiogenesis was recently discov-

ered in MM [109]. In MM deletion of chromosomal 13q, which is known to be an indicator of poor prognosis, was found to be associated with a high bone marrow microvessel density in comparison to MM without 13q deletion [109].

The extracellular matrix (ECM) and enzymes involved in remodeling ECM play an important role in regulating cellular behavior during the angiogenic process [22, 23, 79]. Matrix metalloproteinases (MMP), in particular MMP-2 (gelatinase A) and MMP-9 (gelatinase B) represent an important group of degradative enzymes during angiogenesis [101]. While tumor cells may produce latent proMMPs, in most tumors stromal cells including vascular endothelial cells are the major source of proMMPs that are activated by distinct MMPs or other proteases. In general MMP expression was shown to be upregulated in ALL, AML, NHL and MM [6, 7, 8, 72, 73]. While myeloma cells apparently produce pro-MMP-2 themselves they can stimulate stromal cells to produce pro-MMP2 and -9. On the other hand MMP-7 (matrilysin), involved in MMP-2 activation, is produced by myeloma cells [7].

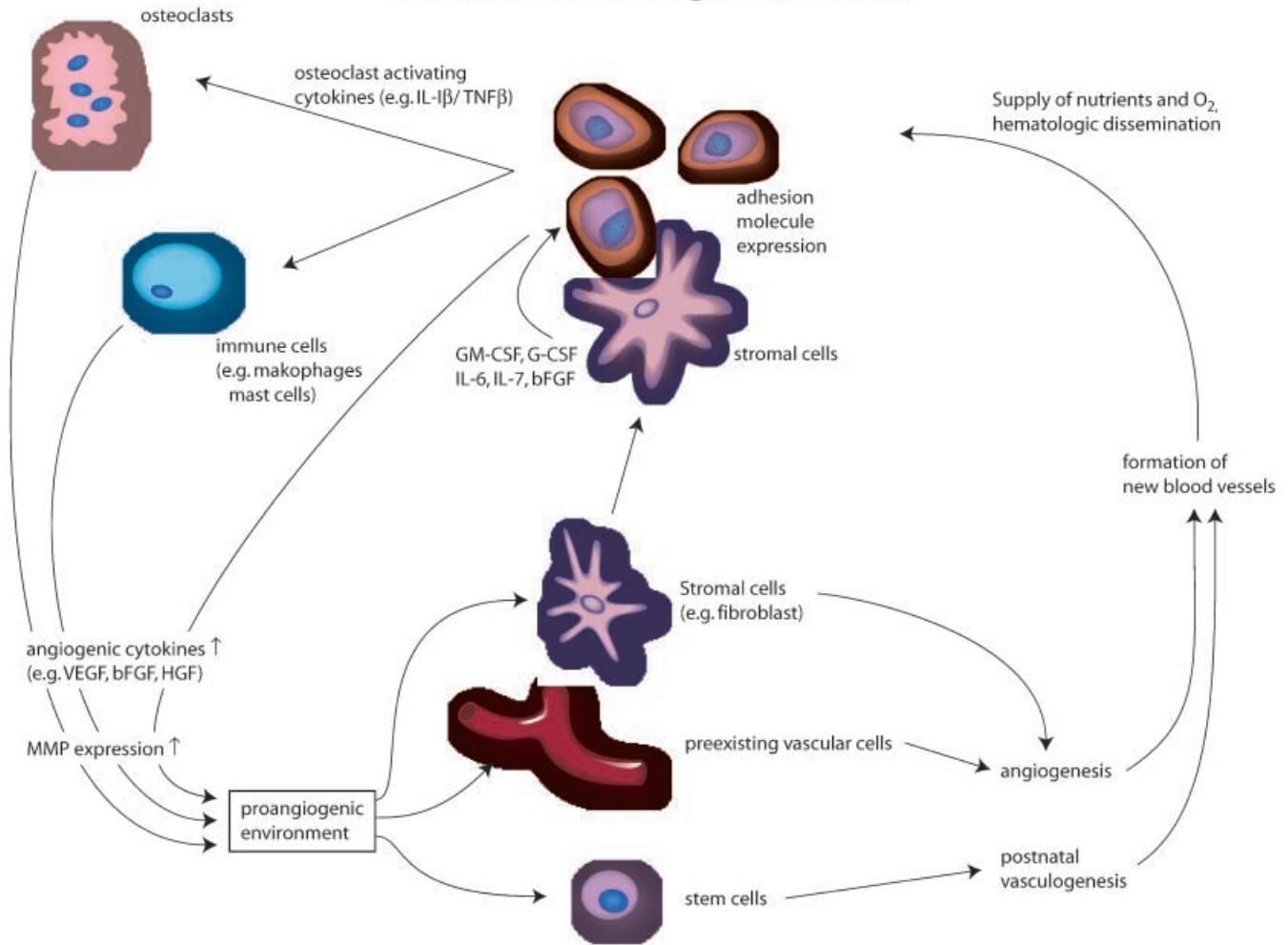
According to recent reports bone marrow-derived endothelial cells can also be involved in angiogenesis, a process that resembles embryonal vasculogenesis [17, 46, 51, 56]. The actual contribution circulating bone marrow-derived endothelial cells make to angiogenesis under physiologic or pathophysiologic conditions is currently under investigation.

In addition to blood vessels the formation of new lymphatic vessels (lymphangiogenesis) can be activated during tumor progression in several animal models of solid tumors. This lymphangiogenesis promotes tumor progression and lymphatic metastasis [65, 114]. Accordingly, expression of VEGF-C, which has been implicated in lymphangiogenesis, was found to be an independent factor in multivariate analysis predicting lymph node metastasis in patients with cervical carcinoma [55]. Results on the relevance of lymphangiogenesis for progression in lymphoma are expected in the near future.

Sparked by the clinical evidence of angiogenesis induction, experimental data have been accumulated by investigating angiogenesis in animal models of hematologic diseases. So far investigations in a number of different animal models have supported the clinical findings [3, 16, 25, 123].

Apart from the function of microvessels to support homeostasis, lymphatic and hematogenous metastasis of tumor cells there may be additional interactions between the endothelial cells as well as other vascular cells and the tumor cells that support tumor growth and metastasis [32]. In MM it could be shown that VEGF produced by myeloma cells stimulates stromal cells to produce IL-6 which acts on myeloma cells in a paracrine loop of activation [32]. In addition to IL-6 other cytokines, namely stem cell factor, Flt-3 ligand, G-CSF, GM-CSF, and IL-7, were also found to be produced by activated endothelial cells and may contribute to a paracrine stimulatory circuit [17]. Expression of VEGF-receptors was also detect-

## Growth of Hematologic Tumor Cells



**Fig. 2** Schematic representation of the stimulatory circuits relevant for angiogenic process in bone marrow and/or lymphatic organs in hematologic malignancies

ed in AML blasts and other hematologic tumor cells allowing a direct effect of VEGF on the tumor cells themselves, thus representing an autocrine loop [1, 2]. Figure 2 provides a schematic representation of angiogenesis in hematological malignancies.

### Angiodiagnosis for prognosis and therapeutic stratification

After angiogenesis induction has been established in all malignant hematologic diseases so far investigated the main focus now is to explore the potential clinical relevance. In NHL an increased vascular density is obviously associated with the more malignant variant of this disease [43, 120]. This view was supported by the finding that increased levels of VEGF and bFGF in peripheral blood of NHL patients are independent adverse prognostic parameters. In this study the simultaneous increase in

bFGF and VEGF describe a group of patients with the shortest overall survival [106, 107]. Several groups have found independently that increased microvessel density detected by immunohistochemistry is an adverse prognostic marker in MM (Table 1) [85, 99]. Bone marrow microcirculation parameters monitored by dMRI were found to be associated with major osteolytic bone involvement in MM. This result indicates that increased bone marrow angiogenesis results in a highly destructive potential for osteolytic myeloma manifestations [82].

Taken together, these data strongly suggest that angiogenesis induction in hematologic diseases has a pathophysiologic relevance for disease progression. The detection of angiogenic activity broadens the diagnostic methods to characterize these diseases and to develop new test systems for improved prognostic scores. These novel markers characterizing the angiogenic process will also be investigated with regard to therapeutic stratification. For example, future studies will reveal whether patients with increased VEGF expression on the cellular level or in clinical samples will benefit more from therapeutics interfering with the VEGF pathway of angiogenesis induction than patients with comparably lower levels.

**Table 2** Angiogenesis inhibitors in clinical trials

Drug	Sponsor	Trial	Mechanism
Drugs that block breakdown of extracellular matrix:			
Marimastat	British Biotech; Annapolis, MD	Phase III, small cell lung, breast cancers	Synthetic inhibitor of matrix metalloproteinases (MMPs)
COL-3	Collagenex; Newtown, PA	Phase I/II, brain	Synthetic MMP inhibitor. Tetracycline® derivative
Neovastat	Aeterna; Québec, Canada	Phase III, renal cell (kidney) cancer, Phase III, non-small cell lung cancer	Naturally occurring MMP inhibitor
BMS-275291	Bristol-Myers Squibb; Wallingford, CT	Phase II/III, Advanced or metastatic non-small cell lung	Synthetic MMP inhibitor
Drugs that inhibit endothelial cells directly:			
Thalidomide	Commercially available, approved for leprosy; Celgene and Lafal; France	Phase I/II, advanced melanoma, multiple myeloma; Phase III non-small cell lung, nonmetastatic prostate, refractory multiple myeloma, renal cancer, Phase II, glioblastoma	Unknown
Squalamine	Magainin Pharmaceuticals; Plymouth Meeting, PA	Phase I, advanced cancers, Phase II, non small cell lung cancer, Phase II, Ovarian cancer	Extract from dogfish or shark liver; inhibits sodium, hydrogen exchanger, NHE3
Endostatin	EntreMed; Rockville, MD	Phase I, solid tumors	Inhibition of endothelial cell growth
Drugs that block activators of angiogenesis:			
SU5416	Sugen; South San Francisco, CA	Phase I / II / III, solid tumors, Phase I, AML, Phase II, multiple myeloma	Blocks VEGF receptor signaling
SU6668	Sugen; South San Francisco, CA	Phase I, advanced solid tumors	Blocks VEGF, FGF, and PDGF receptor signaling
Interferon-alpha Anti-VEGF antibody	Commercially available National Cancer Institute, Bethesda, MD; Genentech, San Francisco, CA	Phase II/III, Advanced solid tumors Phase I, refractory solid tumors	Inhibition of bFGF and VEGF production Monoclonal antibody to vascular endothelial growth factor (VEGF) Bevacizumab
Drugs that inhibit endothelial-specific integrin/survival signaling:			
EMD121974	Merck KGaA; Darmstadt, Germany	Phase I, HIV related Kaposi's sarcoma, Phase I/II, progressive or recurrent anaplastic glioma	Small molecule blocker of alpha-v integrins present on endothelial cell surface
Drugs with non-specific mechanism of action:			
CAI	National Cancer Institute, Bethesda, MD	Phase I, studies in combination against solid tumors, Phase II, ovarian cancer, metastatic renal cell cancer	Inhibitor of calcium influx
Interleukin-12	Genetics Institute; Cambridge, MA	Phase I/II, Kaposi's sarcoma	Up-regulation of interferon gamma and IP-10
IM862	Cytran; Kirkland, WA	Phase I, recurrent ovarian cancer; Phase II, metastatic cancers of the colon and rectal; Phase III, Kaposi's sarcoma	Unknown mechanism

### Antiangiogenic therapy

Experimental evidence has been provided that antiangiogenic therapy is not negatively affected by drug resistance due to the genetic stability of the endothelial cells in contrast to tumor cells [19].

On that basis various strategies for antiangiogenic treatment have been developed [26, 27, 29, 41, 42, 117]. Major principles of antiangiogenic treatment (see also Fig. 2, Table 2) include interference with the following elements of the angiogenic cascade: angiogenic stimulators (e.g., VEGF, bFGF [68]), angiogenic factor recep-

tors (e.g., VEGF-receptor signaling), extracellular matrix interactions (e.g., blocking of endothelial integrins [38]), control of angiogenesis (e.g., inhibiting oncogenes controlling the angiogenic response [100]) and proteolysis (e.g., inhibitors of MMP activity [24, 101]). In addition there are agents that attack the vascular endothelial cell in the angiogenic blood vessel directly (e.g., angiostatin and endostatin [19]). Finally, agents with an unknown mechanism of action (e.g., interleukin-12 [125]) are currently under investigation. An overview of ongoing studies on antiangiogenic treatment is provided by the National Cancer Institute (NCI) (<http://www.cancertri->

als.nci.nih.gov). At the moment there are only a few clinical studies in hematologic malignancies underway in comparison to the large number of antiangiogenic compounds on trial in solid tumors (Table 2).

Experimental evidence for the therapeutic efficiency of antiangiogenic drugs in hematologic neoplasias was provided in several animal models of leukemia and NHL. Endostatin induced a delay in tumor growth in a mouse model of high-grade NHL [16]. When it was applied in combination with cyclophosphamide or anti-CD20 treatment further tumor growth was inhibited as long as the endostatin was present. In contrast, tumors in the control group that did not receive endostatin rapidly progressed.

Functionally blocking anti-VEGF-receptor 2 (VEGFR2) antibodies prolonged survival of SCID mice xenografted with human acute myeloid leukemia cells. However, the antiangiogenic effect of antibodies against VEGFR2 could not be demonstrated unequivocally in this system because the same AML blasts expressed VEGFR2 and the VEGF-receptor blockade induced a 50% inhibition in proliferation [36]. These antibodies also displayed antilymphoma activity in a murine model of a Kaposi's sarcoma-associated herpes virus-infected primary effusion NHL [3].

Recent clinical studies revealed the considerable anti-myeloma effect of Thal which has anti-angiogenic activity [9, 30, 88, 89, 112]. Clinical studies by Barlogie and coworkers using Thal in MM resulted in 37% objective remission in poor risk MM patients [9, 112]. Several studies now provide evidence that Thal increases the efficiency of chemotherapy and dexamethasone treatment in MM [83, 86]. Based on these discoveries the therapeutic value of Thal is currently being tested in virtually every phase of MM including first line treatment.

In addition to the antiangiogenic activity, Thal also affects the immune system and myeloma cells directly [33, 60]. Therefore, a combined mechanism of action *in vivo* should be anticipated.

Clinical studies of inhibitors of the VEGF pathway appear to be particularly promising in malignancies with VEGF receptor expression on the tumor cells such as AML and MM. In fact, Mesters et al. observed the impressive clinical response of a patient with AML on a single agent therapy with the VEGF-tyrosine-kinase inhibitor SU5416 [81].

In recent years several groups provided evidence of the antiangiogenic activity of chemotherapeutics [66]. Induction of apoptosis and inhibition of proliferation and migration of endothelial cells were recognized as mechanisms for the antiangiogenic effects of cytostatic drugs [25, 54, 66]. Further investigation of the antiangiogenic effect of cyclophosphamide's best inhibition was achieved by the "high frequency" application of lower doses of cyclophosphamide in contrast to the "standard" cyclic therapy [25]. These antitumor effects of the "metronomic" scheduling of chemotherapy has been confirmed by others and the synergistic activity was shown in combination with an anti-angiogenic VEGF-receptor-inhibitor [71]. Interestingly, this antiangiogenic schedule was particularly effective in a murine leukemia model [25].

The consequence for clinical application is that scheduling of chemotherapeutics offers another possibility for increasing the therapeutic efficiency of cytostatic drugs as an alternative to dose intensification. Support for the low dose metronomic strategies was recently provided by a report on low-dose Idarubicin therapy in chronic myeloid leukemia (CML) [47]. With regard to novel combination treatment strategies the combination of an angiogenesis inhibitor with the metronomic scheduling of a chemotherapeutic agent appears to be very promising [54, 71].

Radiation was also found to have antiangiogenic effects and a combination of radiation and antiangiogenic treatment with angiostatin was synergistic [78]. Destruction of the stromal compartment is therefore the most likely explanation for the clinical observation that in cases of MM relapse often does not occur in areas of prior irradiation.

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## Perspective

The development of novel treatment strategies and diagnostic procedures for hematologic malignancies depends on the molecular deciphering of the pathophysiologic elements of tumor progression. So far, angiogenesis research has contributed significantly to the pathophysiologic understanding of hematologic disease. The knowledge that is accumulating on the angiogenic response in hematologic neoplasms in their major body compartments, the lymphatic system, and bone marrow will also shed new light on mechanisms of metastasis of solid tumors in these tissues.

Angiodiagnosis will be developed as an additional prognostic tool and may help the clinician in deciding on the most suitable therapy. Antiangiogenic agents can be combined with other novel treatment strategies such as immunologic approaches and agents that interfere with signal transduction.

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