Leukemia (2006) 20, 1356–1357

www.nature.com/leu

EDITORIAL

Tissue factor in hematological malignancies

Leukemia (2006) **20,** 1356–1357. doi:10.1038/sj.leu.2404269

It is now recognized that there is an increasing body of evidence supporting the link between the various components of the coagulation/fibrinolysis systems and angiogenic activity in cancer patients.[1] Platelets contains several positive and negative regulators of angiogenesis (Table 1). Tissue factor (TF), thrombin, fibrinogen, fibrin and plasminogen activator system, as well as platelets, are all able to promote angiogenesis. On the other hand, coagulation inhibitors, as well as proteolytically released domains of hemostatic proteins, are also known to act as angiogenesis inhibitors. Judah Folkman speculated that 'during the first days of wound healing as nascent clot bridges and stabilizes the vessel defect, any initiation of angiogenesis directed by platelet-derived angiogenic stimulators, or by thrombin and fibrin, must be counteracted'.[2]

TF is a cell-associated receptor for coagulation factor VII/VIIa, an interaction known to activate the coagulation cascade. At the same time, TF is also known as a mediator of intracellular signaling events that can alter gene expression patterns and cell behavior. It has become clear that TF functions as a cytokine-like receptor and this notion was confirmed by the discovery of coagulation-independent actions of TF, including regulation of tumor growth, angiogenesis, as well as regulation of inflammation and sepsis.[3]

Both clotting-dependent and -independent mechanisms of TF-induced angiogenesis have been elucitated.[4] Clotting-dependent induction of tumor angiogenesis is primarily mediated by TF-induced generation of thrombin and subsequent deposition of cross-linked fibrin. A cross-linked fibrin network provides a provisional proangiogenic matrix that facilitates blood vessel infiltration. Clotting-independent mechanisms of TF-induced tumor angiogenesis have also been described, mediated primarily by the cytoplasmatic tail of the TF receptor. Both aspects of TF activity are of possible relevance to tumor growth, metastasis and angiogenesis, including upregulation of vascular endothelial growth factor (VEGF). TF status is known to affect expression of other angiogenesis stimulators, such as fibroblast growth factor-4 (FGF-4) and interleukin-8 (IL-8), and inhibitors, such as thrombospondin-1 and -2 (TSP-1, TSP-2).[5] TF upregulation is often observed on the surfaces of tumor-associated endothelial cells, inflammatory cells, and particularly on cancer cells themselves. In the last case, high TF levels may be associated with poor prognosis and parallel clinical and genetic tumor progression.

In the present issue of *Leukemia,* Lòpez-Pedrera *et al.*[6] publish a review article focused on the current knowledge about

Table 1 Positive and negative regulators of angiogenesis carried by platelets

Positive
Vascular endothelial growth factor (VEGF)
Fibroblast growth factor-2 (FGF-2)
Hepatocyte growth factor (HGF)
Angiopoietin-1
Platelet derived growth factor (PDGF)
Epidermal growth factor (EGF)
Vitronectin
Fibronectin
Fibrinogen
Heparanase
Negative
Thrombospondin
Transforming growth factor beta-1 (TGF-β1)
Plasminogen (Angiostatin)
High molecular weight kininogen (domain-5)
Fibronectin (45 kD fragment)
Alpha-2 antiplasmin (fragment)
Beta-thromboglobulin
Tissue inhibitors matrix of metalloproteases-1 and -2 (TIMP 1, 2)

Table 2 Historical review of angiogenesis involvement in hematological malignancies

Angiogenesis	*References*
First evidence of bone marrow angiogenesis in MM	—
High correlation between the extent of bone marrow angiogenesis and plasma cell proliferation	7
Role of bone marrow microenvironment in MM	8
First evidence of bone marrow angiogenesis in B-NHL	—
High correlation between the extent of bone marrow angiogenesis and B-NHL grading	9
First evidence of increased bone marrow microvessel density in ALL	10
Role of mast cells tryptase-positive in angiogenic cascade in B-NHL, MM, and B-CLL	11–13
Induction of angiogenesis by plasma cells secretion of FGF-2 and MMP-2 in active MM	14
First evidence of angiogenesis involvement in the pathogenesis of B-CLL	15
High bone marrow and serum levels of angiogenic cytokines in MM	16
High expression of VEGF in plasma cells, myeloid and monocyte precursors	17
High synthesis of MMP-2 and MMP-9 by B-CLL cells	18
Detailed phenotypic, genetic and functional characterization of bone marrow endothelial cells from patients with MM	19
Demonstration of a preangiogenic phase in MM characterized by high amount of CD45-cells	20

Abbreviations: ALL, acute lymphocytic leukemia; B-CLL, B cell chronic lymphocytic leukaemia; B-NHL, B cell non-Hodgkin's lymphomas; MM, multiple myeloma.

the mechanisms by which TF promotes angiogenesis and invasiveness in hematological malignancies. The role of angiogenesis in the growth and survival of leukemias and other hematological malignancies has been rendered evident since 1994 in a series of demonstrations showing that the progression of several forms is clearly related to their degree of angiogenesis (Table 2).

Lymphomas and some other hematological malignancies, such as multiple myeloma and myeloproliferative disorders, described to be associated to the development of thrombotic events, have now been reported in relation to their association with aberrant TF expression. The incidence of severe complications, such as disseminated intravascular coagulation (DIC) in malignant lymphoma might involve elevated cytokine expression by lymphoma cells stimulating the expression of TF in blood cells or surrounding tissue. It has been described an increased expression of TF in patients with acute myeloid leukemia (AML), accounting for an increased risk of thrombohemorragic alterations. Both TF and VEGF, remarkably elevated and simultaneously expressed in blast AML cells, might determine an increase in tumor angiogenesis. These data have been confirmed by genomics and proteomics studies demonstrating that blast samples exhibited increased expression of both TF and VEGF. In multiple myeloma and myeloproliferative disorders the development of thrombotic events occurs, without any relationship with TF expression.

Upregulation of TF in cancer presents itself as an attractive therapeutic strategy.[5] Direct targeting of TF in cancer should be considered in combination with other treatment modalities such as oncogene-directed therapies, antiangiogenic agents and anticancer chemotherapy. Moreover, anticoagulants, such as low molecular weight heparin, may act to prevent these complications both by interfering with TF-mediated activation of clotting and by directly downregulating angiogenesis. Thus, the use of retinoids for their differentiating activity in conjunction with specific antiangiogenic agents, such as anti-VEGF antibodies, would be useful in ameliorating both the angiogenesis and the coagulopathy seen in acute promyelocytic leukemia and other types of myeloid leukemias.

D Ribatti
Department of Human Anatomy and Histology, University of Bari Medical School, Bari, Italy
E-mail ribatti@anatomia.uniba.it

References

1 Wojtukiewicz MZ, Sierko E, Rak J. Contribution of the hemostatic system to angiogenesis in cancer. *Semin Thromb Hemost* 2004; **30**: 5–20.
2 Browder T, Folkman J, Pirie-Shepherd S. The hemostatic system as a regulator of angiogenesis. *J Biol Chem* 2000; **275**: 1521–1524.
3 Versteeg HH, Peppelenbosch MP, Spek CA. Tissue factor signal transduction in angiogenesis. *Carcinogenesis* 2003; **24**: 1009–1013.
4 Fernandez PM, Patierno SR, Rickles FR. Tissue factor and fibrin in tumor angiogenesis. *Semin Thromb Hemost* 2004; **30**: 31–44.
5 Rak J, Milsom C, May L, Klement P, Yu J. Tissue factor in cancer and angiogenesis: the molecular link between genetic tumor progression, tumor neovascularization, and cancer coagulopathy. *Semin Thromb Hemost* 2006; **32**: 54–70.
6 Lòpez-Pedrera C, Barbarroja N, Dorado G, Siendones E, Velasco F. Tissue factor as an effector of angiogenesis and tumor progression in hematological malignancies. *Leukemia* 2006.
7 Vacca A, Ribatti D, Roncali L, Ranieri G, Serio G, Silvestris F *et al.* Bone marrow angiogenesis and progression in multiple myeloma. *Br J Haematol* 1994; **87**: 503–508.
8 Klein B, Zhang X, Lu Z. Interleukin-6 in human multiple myeloma. *Blood* 1995; **85**: 863–872.
9 Ribatti D, Vacca A, Nico B, Fanelli M, Roncali L, Dammacco F. Angiogenesis spectrum in the stroma of B-cell non-Hodgkin's lymphomas. An immunohistochemical and ultrastructural study. *Eur J Haematol* 1996; **56**: 45–53.
10 Perez-Atayde AR, Sallan SE, Tedrow U, Connors S, Allured EN, Folkman J. Spectrum of tumor angiogenesis in the bone marrow of children with acute lymphocytic leukemia. *Am J Pathol* 1997; **150**: 815–821.
11 Ribatti D, Nico B, Vacca A, Marzullo A, Calvi N, Roncali L *et al.* Do mast cells help to induce angiogenesis in B-cell non-Hodgkin's lymphomas? *Br J Cancer* 1998; **77**: 1900–1906.
12 Ribatti D, Vacca A, Nico B, Quondamatteo F, Ria R, Minischetti M *et al.* Bone marrow angiogenesis and mast cell density increase simultaneously with progression of human multiple carcinoma. *Br J Cancer* 1999; **79**: 451–455.
13 Ribatti D, Molica S, Vacca A, Nico B, Crivellato E, Roccaro AM *et al.* Tryptase-positive mast cells correlate positively with bone marrow angiogenesis in B-cell chronic lymphocytic leukemia. *Leukemia* 2003; **17**: 1428–1430.
14 Vacca A, Ribatti D, Presta M, Minischetti M, Iurlaro M, Ria R *et al.* Bone marrow neovascularization, plasma cell angiogenic potential, and matrix metalloproteinase-2 secretion parallel progression of human multiple myeloma. *Blood* 1999; **93**: 3064–3073.
15 Molica S, Vitelli C, Levato D, Gandolfo GM, Liso V. Increased serum levels of vascular endothelial growth factor predict risk of progression in early B-cell chronic lymphocytic leukemia. *Br J Haematol* 1999; **107**: 605–610.
16 Di Raimondo FD, Azzaro MP, Palumbo GA, Bagnato S, Giustolisi G, Floridia PM *et al.* Angiogenic factors in multiple myeloma: higher levels in bone marrow than in peripheral blood. *Haematologica* 2000; **85**: 800–805.
17 Bellamy WT. Expression of vascular endothelial growth factor and its receptors in multiple myeloma and other hematopoietic malignancies. *Semin Oncol* 2001; **28**: 551–559.
18 Bauvois B, Dumont J, Mathiot C, Kolb JP. Production of matrix metalloproteinase-9 in early C-CLL: suppression by interferons. *Leukemia* 2002; **16**: 791–798.
19 Vacca A, Ria R, Semeraro F, Merchionne F, Coluccia M, Boccarelli A *et al.* Endothelial cells in the bone marrow of patients with multiple myeloma. *Blood* 2003; **102**: 3340–3348.
20 Asosingh K, De Raeve H, Menu E, van Riet I, Van Marck E, van Camp B *et al.* Vanderkerken K. Angiogenic switch during 5T2MM murine myeloma tumorigenesis: role of CD45 heterogeneity. *Blood* 2004; **103**: 3131–3137.