The Role of VEGF in Oncology: Effects on Hemostasis and Thrombosis

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Angiogenesis is essential for tumor growth and metastasis [1]. One of the key players in the angiogenic process is vascular endothelial cell growth factor (VEGF), which exerts its effects through in particular VEGFR-1 (Flt-1 murine homologue) and VEGFR-2 (KDR human homologue; Flk-1 murine homologue) located on endothelial cells (ECs) [2]. These well known effects include increased permeability, proliferation and migration of ECs. However, VEGF also affects hemostatic properties of ECs by inducing the rapid release of von Willebrand factor (vWF), by increasing the expression of tissue factor (TF) and thrombomodulin (TM), and by modifying fibrinolysis due to the stimulation of the expression levels of tissue-plasminogen

activator (t-PA), urokinase-plasminogen activator (u-PA), plasminogen activator inhibitor-1 (PAI-1) and the receptor for u-PA (u-PAR) [3–13]. VEGF stimulated ECs furthermore promote adhesion and activation of platelets [9]. On the other hand, platelets are transporters of among other factors VEGF and have most likely a role in tumor induced angiogenesis [14, 15]. This hypothesis has been confirmed by the finding of very high concentrations of both VEGF and coagulation factors in tumor fluid of soft tissue sarcomas [16]. There is growing evidence that coagulation, platelets and angiogenesis are indistinguishable involved in tumor growth.

References

- 1 Hanahan D, Folkman J: Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. *Cell* 1996;86:353–364.
- 2 Carmeliet P, Jain RK: Angiogenesis in cancer and other diseases. *Nature* 2000;407:249–257.
- 3 Li W, Keller G: VEGF nuclear accumulation correlates with phenotypical changes in endothelial cells. *J Cell Sci* 2000;113:1525–1534.
- 4 Brock TA, Dvorak HF, Senger DR: Tumor-secreted vascular permeability factor increases cytosolic Ca^{2+} and von Willebrand factor release in human endothelial cells. *Am J Pathol* 1991;138: 213–221.
- 5 Zanetta L, Marcus SG, Vasile J, et al: Expression of von Willebrand factor, an endothelial cell marker, is up-regulated by angiogenesis factors: A potential method for objective assessment of tumor angiogenesis. *Int J Cancer* 2000;85:281–288.
- 6 Clauss M, Gerlach M, Gerlach H, et al: Vascular permeability factor: A tumor-derived polypeptide that induces endothelial cell and monocyte procoagulant activity, and promotes monocyte migration. *J Exp Med* 1990;172:1535–1545.
- 7 Camera M, Giesen PLA, Fallon J, et al: Cooperation between VEGF and $\text{TNF-}\alpha$ is necessary for exposure of active tissue factor on the surface of human endothelial cells. *Arterioscler Thromb Vasc Biol* 1999;19:531–537.

- 8 Mechtcheriakova D, Wlachos A, Holzmüller H, et al: Vascular endothelial cell growth factor-induced tissue factor expression in endothelial cells is mediated by EGR-1. *Blood* 1999;93:3811–3823.
- 9 Verheul HM, Jorna AS, Hoekman K, et al: Vascular endothelial growth factor-stimulated endothelial cells promote adhesion and activation of platelets. *Blood* 2000;96:4216–4221.
- 10 Calnek DS, Grinnell BW: Thrombomodulin-dependent anticoagulant activity is regulated by vascular endothelial growth factor. *Exp Cell Res* 1998;238:294–298.
- 11 Pepper MS, Ferrara N, Orci L, et al: Vascular endothelial growth factor (VEGF) induces plasminogen activators and plasminogen activator inhibitor-1 in microvascular endothelial cells. *Biochem Biophys Res Commun* 1991;181:902–906.
- 12 Mandriota SJ, Pepper MS: Vascular endothelial growth factor-induced in vitro angiogenesis and plasminogen activator expression are dependent on endogenous basic fibroblast growth factor. *J Cell Sci* 1997;110:2293–2302.
- 13 Kroon ME, Koolwijk P, Vermeer MA, et al: Vascular endothelial growth factor enhances the expression of urokinase receptor in human endothelial cells via protein kinase C activation. *Thromb Haemost* 2001;85:296–302.
- 14 Verheul HM, Hoekman K, Luykx-de Bakker S, et al: Platelet: Transporter of vascular endothelial growth factor. *Clin Cancer Res* 1997;3:2187–2190.
- 15 Pinedo HM, Verheul HM, D'Amato RJ, et al: Involvement of platelets in tumour angiogenesis? *Lancet* 1998;352:1775–1777.
- 16 Verheul HM, Hoekman K, Lupu F, et al: Platelet and coagulation activation with vascular endothelial growth factor generation in soft tissue sarcomas. *Clin Cancer Res* 2000;6:166–171.