Endothelial Cell Tissue Factor : Role in Thrombotic Disorders

Wanida Wongtiraporn, M.D.*

INTRODUCTION

Endothelial cells line the lumen of blood vessels and form a barrier between internal constituents and the extra-vascular tissues. It constitutes approximately 1% of body mass and a surface area of approximately 5,000 m^2.[1] The normal life-span of a human endothelial cell is around 30 years.[1] Endothelial cells are now recognized as playing a critical role in blood vessel wall regulation. In addition to the control of vascular permeability, vascular tone and the inflammatory response, endothelial cells synthesize and release a variety of biologically active substances that provide a balance between prothrombotic and antithrombotic states. The prothrombotic state is mediated by the synthesis of von Willebrand factor, plasminogen activator inhibitor, tissue factor and platelet activating factor, whereas the anti-thrombotic state entails the production of prostacyclin, tissue plasminogen activator, thrombomodulin, nitric oxide and tissue factor pathway inhibitor.[2-7]

In pathological states, circulating mediators or vascular damage can disturb endothelial function, leading to an imbalance between prothrombotic and anti-thrombotic products of endothelial cells. This imbalance is believed to be one component of the pathogenesis of thrombotic disorders. This current review will focus on endothelial tissue factor and its role in thrombotic disorders.

Endothelial cell tissue factors

Tissue factor (TF) is a 47 kDa integral membrane glycoprotein that functions as the primary cellular initiator of blood coagulation. Human TF consists of three domain : a short cytoplasmic domain of 19 residues, a single transmembrane domain of 23 residues and a large extracellular domain of 219 residues.[8] TF serves as the receptor and essential cofactor for factor VII and VIIa.[9] The VIIa and TF complex initiates the coagulation cascade with subsequent activation of factor X and IX.[9] TF is constitutively expressed by several extravascular cell types and inducibly expressed within the vasculature by monocytes and endothelial cells. As a potent initiator of blood coagulation, TF expression initiates thrombotic episodes associated with various diseases including atherosclerosis, septic shock and cancer.

With the advance of culture techniques, endothelial cells can be studied extensively *in vitro*. Most of the experiments concerning endothelial TF are performed in human umbilical vein endothelial cells (HUVEC). Unlike extravascular cells, TF cannot be demonstrated in normal endothelial cells. In culture, endothelial cells express very little TF. Nevertheless, upon exposure to pathological mediators, endothelial cells can be significantly up-regulated in respect to abundance of mRNA and TF protein.[8] The TF promoter has binding sites for several transcription factors, including Spl, Egr-1, AP-1 which regulate both basal and inducible expression of TF.[8] Activators of these transcription factors can stimulate TF expression.

Cytokines and TF synthesis

It has been shown that upon exposure to cytokines, endothelial cells undergo profound changes and express TF. When cultured with lipopolysaccharides, TF activity of HUVEC increases several-fold in a dose-dependent response.[10-12] Most of this activity is expressed on the surface of

*Department of Clinical Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700.

HUVEC.[11,12] The increase in TF activity is observed as early as 2 hours with maximal expression at 6 hours and subsequent return to baseline at 24 hours.[10-12] A temporary rise in TF activity of endothelial cells may contribute to the pathogenesis of DIC in gram-negative septicemia.

Interleukin 1 (IL-1) is able to induce TF expression of HUVEC, as well. IL-1 infusion resulted in a time and dose-dependent induction of TF. TF activity increased more than 10-fold by 3-5 hours and reached a maximum activity at 5 hours with a decline to baseline at 24 hours.[13,14] Like IL-1, induction of TF by tumor necrosis factor (TNF) is concentration dependent and time dependent. A rapid rise in TF to peak activity is evident at 4 hours and a decline toward basal levels is seen by 24 hours.[15] Moreover, the effects of TNF and IL-1 were found to be additive.[15] Action of TNF and IL-1 on endothelial cells *in vivo* may contribute to the development of thrombotic and inflammatory reactions.

Lipoproteins and TF synthesis

Numerous studies have revealed that expression of TF is induced in HUVEC by incubation with lipoproteins. Within 12 hours of stimulation, the lysate of HUVEC incubated with very low density lipoprotein (VLDL) expresses about a four-fold increase in TF activity compared with control cells.[16-18] In comparison to VLDL, the lysate of HUVEC incubated with low density lipoproteins (LDL) shows a lesser increase in TF activity and there is no increase in TF activity of the lysate of HUVEC incubated with high density lipoproteins (HDL).[16-19] It is concievable, therefore, that VLDL and LDL can be direct risk factors for thrombotic diseases.

Plasma factors and TF synthesis

In the presence of plasma, TF activity of HUVEC is significantly increased. The induction of TF by plasma factors is even higher when incubated with plasma from patients with disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP) and positive lupus anticoagulant (LA).[20] Autoantibodies to endothelial cell (AECA) from patients with systemic lupus erythrematosus (SLE) have been shown to induce the expression of TF on HUVEC, as well.[21] Enhanced TF production in endothelial cells by plasma factors may play an important role in the pathogenesis of DIC, TTP and deep vein thrombosis in LA-positive patients.

Plasma TF antigen in thrombotic disorders

In normal, healthy individuals, plasma TF antigen can be detected at low levels. In DIC patients, plasma TF antigen is significantly higher. However, in some DIC patients, the plasma TF antigen is not high.[22] Moreover, plasma TF antigen is not increased in patients with TTP or LA who have thrombosis.[23]

TF and atherosclerosis

The role of TF has been demonstrated in atherosclerosis. TF accumulated in experimentally injured vessels and atherosclerotic plaques. The largest amount of TF is presented in the lipid core, the most thrombogenic component of atherosclerotic plaques. The endothelial cells overlying the atheromatous plaque also stain for TF.[24] TF in atheromatous plaques may be important in the thrombotic complications of atherosclerotic heart disease.

REFERENCES

1. Toborek M, Kaiser S. Endothelial cell functions. Relationship to atherogenesis. Basis Res Cardiol 1999; **94:** 295-314.
2. Jaffe E A, Hoyer LW, Nachman RL. Synthesis of anti-*hemophilic factor antigen* by cultured human endothelial cells. J Clin Incest 1974 ; **52:** 2754-2764.
3. Loskutoff D J, van Mourik JA, Erickson LA, Lawrence D. Detection of an unusually stable fibrinolytic inhibitor produced by bovine endothelial cells. Proc Natl Acad Sci USA 1983; **80:** 2956- 960.
4. Moncada S, Gryglewski R, Bunting S, Vane JR. An enzyme isolated from arteries transforms prostaglandin endoperoxides to an unstable substance that inhibits platelet aggregation. Nature 1976; **263:** 663-665.
5. Levin E G, Loskutoff DJ. Cultured bovine endothelial cells produce both urokinase and tissue type plasminogen

activator. J Cell Biol 1982; **94:** 631-636.
6. Stern D, Brett J, Harris K, Nawroth P. Participation of endothelial cells in the protein C – protein S anticoagulant pathway: the synthesis and release of protein S. J Cell Biol 1986; **102:** 1971-1978.
7. Esmon CT, Owen WG. Identifcation of an endothelial cell cofactor for thrombin-catalyzed activation of protein C. Proc Natl Acad Sci USA 1981; **78:** 2249-2252.
8. Mackman N. Regulation of the tissue factor gene. The FASEB J 1995; **9:** 883-889.
9. Martin D, Boys CWG, Ruf W. Tissue factor: molecular recognition and cofactor function. The FASEB J 1995; **9:** 853-859.
10. Moldow CF, Bach R R, Staskus K, Rick PD. Induction of endothelial tissue factor by endotoxin and its precursors. Thromb Haemostas 1994; **70:** 702-706.
11. Brox JH, Osterud B, Bjorklid E, Fenton II JW. Production and availability of thromboplastin in endothelial cells: the effects of thrombin, endotoxin and platelets. Br J Haematol 1984; **57:** 239–246.
12. Moore RL, Andreoli SP, Ksmon NL, Eamon CT, Bang ND. Endotoxin enhances tissue factor and suppresses thrombomodulin expression of human vascular endothelium in vitro. J Clin Invest 1987; **79:** 124-130.
13. Schorer AE, Kaplan ME, Rao GHR, Moldow CF. Interleukin – 1 stimulated endothelial tissue factor production and expression by a prostaglandin – independent mechanism. Thromb Haemostas 1987; **56:** 256-259.
14. Nawroth PP, Handley DA, Esmon CT, Stern DM. Interleukin 1 induces endothelial cell procoagulant while suppressing cell-surface anticoagulant activity. Proc Natl Acad Sci USA 1986; **83:** 3460-3464.
15. Bevilacqua MP, Prober JS, Majeau GR, Fiers W, Cotran RS, Gimbrone MA Jr. Recombinant tumor necrosis factor induces procoagulant activity in cultured human vascular endothelium: characterization and comparison with the actions of interleukin-1. Proc Natl Acad Sci USA 1986; **83:** 4533-4537.
16. Weis JR, Pitas RE, Wilson BD, Rodgers GM. Oxidized low-density lipoprotein increases cultured human endothelial cell tissue factor activity and reduces protein C activation. The FASEB J 1991; **5:** 2459-2465.
17. Drake TA, Hannani K, Fei H, Lavi S, Berliner JA. Minimally oxidized low-density lipoprotein induces tissue factor expression in cultured human endothelial cells. Am J Pathol 1991; **138:** 601-607.
18. Henriksen T, Evenscn SA, Carlander B. Injury to cultured endothelial cells induced by low density lipoproteins: protection by high density lipoproteins. Scand. J Clin Lab Invest 1979; **39:** 369-375.
19. Kaneko T, Waada H, Wakita Y, et al. Enhance tissue factor activity and plasminogan activator inhibitor-1 antigen in human umbilical vein endothelial cells incubated with lipoproteins. Blood Coag Fibrinol 1994; **5:** 385-392.
20. Wada H, Tamaki S, Kaneko T, et al. Plasma from patients with disseminated intravascular coagulation or thrombotic thrombocytopenic purpura enhances tissue factor activity in human umbilical vein endothelial cells. J Am Med Assoc 1992; **8 (Suppl):** 25-29.
21. Tannenbaum SH, Finko R, Cines DB. Antibody and immune complexes induce tissue factor production by human endothelial cells. J Immunol 1986; **137:** 1532-1537.
22. Wada H, Nakase T, Nakaya T, et al. Elevated plasma tissue factor antigen level in patients with disseminated intravascular coagulation. Am J Hematol 1994; **45:** 232-236.
23. Wada H, Wakita Y, Shiku H. Tissue factor expression in endothelial cells in health and disease. Blood Coag Fibrinol 1995; **6 (Suppl 1):** 26-31.
24. Taubman M, Fallon JT, Schecter AD, et al. Tissue factor in the pathogenesis of atherosclerosis. Thromb Haemost 1997; **78:** 200-204.