Trends in Cardiovascular Medicine 26 (2016) 297–303

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Tissue factor as a link between inflammation and coagulation

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ABSTRACT

Due to its receptor activity for factor VII, tissue factor (TF) is primary initiator of the blood coagulation cascade and ensures rapid hemostasis in case of organ damage. Inflammatory cytokines, such as tumor necrosis factor-α or interleukins, strongly induce expression of both full-length TF as well as the alternatively spliced TF in endothelial and blood cells. Beyond its role in hemostasis, TF also has signaling activity and promotes pleiotropic inflammatory responses via protease-activated receptors in concert with other coagulation factors. Alteration of TF expression and TF alternative splicing provides an effective means to change the endothelial phenotype and modulate inflammatory responses of the vessel.

Key words: Tissue factor, Inflammation, Coagulation, Vessel, Endothelium.

Introduction

Being the receptor for factor VIIa tissue factor (TF), also termed coagulation factor III (F3), is the primary initiator of the extrinsic blood coagulation cascade [1]. Upon injury of the vessel and surrounding tissue, TF is exposed to blood coagulation factors. The complex TF:VIIa catalyzes the proteolytic activation of the coagulation factors X and IX leading to thrombin generation and subsequently fibrin and thrombus formation [2]. Beside the main procoagulant activity of TF, engagement of ligands, such as protease-activated receptors (PARs), also promotes signal transduction of inflammatory cascades in the vasculature. Extensive research on TF biology within the last decade revealed miscellaneous functions in the circulating blood and the vessel wall. The aim of this review is to highlight the interplay of TF and associated factors leading to activation and maintenance of the inflammation-coagulation axis of the vessel.

Structure of tissue factor

The F3 precursor transcript includes 6 exons. Upon constitutive splicing, the mRNA is translated into full-length (fl)TF, a 47 kDa transmembrane glycoprotein. The flTF protein comprises an extracellular domain of 219 amino acids (aa), a transmembrane region of 23 aa, and a 21 aa cytoplasmic tail. flTF shows sequence and structural homologies to other receptors, such as the Interferon (IFN)-α, IFN-γ, and Interleukin (IL)-10 receptor, which makes it a member of the class 2 cytokine receptor family. Protein structures include 2 fibronectin type III repeats (termed D1 and D2), 2 disulfide bridges, and 3 glycosylation sides. Protein folding of flTF causes D1 and D2 to build a rigid interface region. Systematic mutagenesis and the 3-dimensional structure of the TF:VIIa complex revealed a binding of factor VII within this interface, which also involves the disulfide bridge of the D2 module [3].

The authors have indicated that there are no conflicts of interest.

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http://dx.doi.org/10.1016/j.tcm.2015.12.001
1050-1738/

Expression and function of the TF isoforms

In 2003, while investigating granulocyte differentiation, Bogdanov et al. [4] revealed the existence of another TF isoform. Alternative splicing of the TF transcript elicits a loss of exon 5 entailing a frame shift in the open reading frame. This yields the soluble 206 aa alternatively spliced (as)TF, which lacks the transmembrane domain resulting in a unique 40 aa C-terminus [4]. Since the discovery of asTF, it has become clear that both flTF and its isoform are distinct proteins sharing similarities and important differences.

Full-length TF

flTF is expressed in a vast range of tissues accounting for its crucial role in homeostasis of the body. Large amounts were found in the brain, lung, placenta, heart, testis, and kidneys [5]. Depending on the cell type, expression can be either constitutive or inducible. flTF exerts its main physiologic function in maintaining hemostasis and vessel integrity [6]. Therefore, perivascular cells, including fibroblasts, pericytes, or epithelial cells constitutively express flTF supporting the concept of a hemostatic envelope. Accordingly, TF knockout mice were found non-viable and die early in utero due to severe extravasation of blood cells and abnormal circulation [6]. Moreover, TF is also involved in important processes, such as heart hemostasis, angiogenesis, wound healing, apoptosis, and proliferation [7–10].

Vascular cells, such as smooth muscle cells (SMCs), endothelial cells (ECs) or blood cells, do not express considerable amounts of flTF in a quiescent state, but can be induced via different factors [11]. Upon contact with blood, flTF becomes exposed to blood-borne zymogen coagulation factors. In the presence of flTF plasma factor VII is bound to form a flTF:VII complex. This allows factor VII to be readily activated by the factors X, IX, and VII. The flTF:VIIa activates factor X to Xa, which then converts pro-thrombin into thrombin together with its cofactor Va. Finally, thrombin generation causes fibrin formation, platelet activation, and thrombus deposition [2,12]. The vasculature provides a functional pool of flTF and carotid arteries of mice exert factor Xa generation in a chromogenic assay [13].

flTF is not only found in perivascular cells, but is also present in the blood (blood-borne flTF). Here, flTF is mainly part of circulating extracellular vesicles (EVs) derived from ECs, SMCs, mononuclear cells, or platelets [14]. Blood-borne TF is procoagulant and causes clot formation on pig arterial media and on collagen-coated slides independent from vessel-associated TF [15]. Monocytes are considered to be the main source of blood-borne flTF.

Beside, thrombocytes were found to possess small amounts of flTF in their α-granules due to incorporation of monocyte-derived EVs with the platelet membrane through interaction with adhesion molecules, such as CD15 [1,14,16].

Beyond the protective role in hemostasis, high levels of TF were found to be associated with cardiovascular diseases including diabetes mellitus, atherosclerosis, or acute coronary syndromes [17–20]. Moreover, various cancer diseases, which also confer a procoagulant state, were found to be associated with elevated levels of flTF [7,21–23] The contribution of different cellular flTF pools in the vessel and blood to the initiation and propagation of thrombosis remains controversial. Transplantation of bone marrow from animals with impaired TF expression into wild type mice resulted in thrombi of smaller size with reduced TF accumulation upon microvascular injury in the chimera [24]. Abrogation of vessel wall TF in the presence of hematopoietic TF expression led to impaired thrombus initiation in the same study. However, a model of macrovascular thrombosis demonstrated the vasculature to be the main source of TF leading to vessel occlusion [13]. While a SMC-specific TF deletion reduced the vessel occlusion following ferric chloride-induced carotid injury [25], the role of EC-derived TF has not been addressed in this setting.

Vascular TF expression therefore seems critical for triggering and sustaining thrombotic events. Yet, the contribution of all potential vascular TF sources to arterial thrombosis remains to be elucidated in further studies using conditional knockouts.

Alternatively spliced TF

Tissue-specific regulation of splicing events determines the expression of the soluble asTF. Generally, asTF is broadly expressed and the detection pattern resembles that of flTF. Within the lung, a much higher asTF:flTF mRNA ratio was observed compared to other tissues [4,26]. asTF is also present in the vasculature and can be detected in ECs and SMCs upon induction as well as in blood [4,11,27]. Due to the frequency of alternative splicing under normal conditions asTF is generally expressed in lower amounts compared to flTF [28].

A hallmark of asTF is its reduced procoagulability compared to the full-length protein [27]. Albeit little factor Xa-generation in the presence of asTF could be observed and pancreatic cancer cells overexpressing asTF had heightened procoagulant activity [4,29], Sluka et al. [30] found that mice expressing murine asTF in the absence of flTF did not exhibit a relevant procoagulant activity in plasma clotting assays. In addition, supernatants derived from cancer cells that contained asTF showed markedly decreased TF activity compared to flTF-bearing EVs [31]. Due to the low-procoagulant activity, tissue-specific changes in the TF isoform expression may alter cellular thrombogenicity under certain conditions [27,32].

asTF is involved in miscellaneous processes, such as cell survival, angiogenesis, proliferation, leukocyte diapedesis, and metastasis [9,26,33,34]. Altered expression of asTF during different stages of the heart suggests a role in tissue development [28]. These changes may be due to alternative splicing during heart development. Since mice with reduced expression (~1%) of TF show a normal heart development little amounts of asTF may be sufficient to control these processes [35].

Inflammation drives tissue factor expression in the vessel and blood

At rest, the endothelium represses TF expression and releases anti-thrombogenic factors, such as TF pathway