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Cellular Sources of Tissue Factor in Endotoxemia and Sepsis

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Abstract

Sepsis is a systemic host response to infection by pathogenic microorganisms. Activation of the coagulation cascade during endotoxemia and sepsis leads to disseminated intravascular coagulation. This review focuses on tissue factor expression by hematopoietic and non-hematopoietic cells and its contribution to the activation of coagulation during endotoxemia and sepsis.

Keywords

Tissue factor; cell type; sepsis; endotoxemia; disseminated intravascular coagulation

Introduction

Tissue factor is the primary initiator of the coagulation cascade[1]. Upon vascular damage or induction of TF expression within vasculature and blood cells, TF comes into the contact with blood. This leads to the formation of the TF:FVIIa complex that activates both FX and FIX, with subsequent thrombin generation, fibrin deposition and activation of platelets[1]. Disseminated intravascular coagulation (DIC) results from a pathological activation of coagulation in response to a variety of diseases, including endotoxemia and sepsis[2]. DIC is associated with a poor prognosis and a high mortality rate. The widespread activation of coagulation leads to the formation of occlusive thrombi within the microvasculature leading to ischemic events and impaired perfusion in multiple organs[2]. Sepsis is also associated with a consumptive coagulopathy and thrombocytopenia resulting in bleeding. In critically ill patients, all of these events may contribute to the development of multisystem organ failure and subsequent mortality[2]. This review focuses on the identification of cellular sources of TF that contribute to the activation of coagulation in endotoxemia and sepsis.

Role of the TF:FVIIa complex in endotoxemia and sepsis

Many studies have demonstrated that inhibition of the TF:FVIIa complex attenuates coagulopathy and reduces morbidity in sepsis. In 1990, Rapaport's group first showed that treatment with anti-TF antibody reduced disseminated intravascular coagulation in endotoxemic rabbit[3]. Taylor and colleagues then demonstrated that pretreatment with an anti-TF monoclonal antibody not only attenuated the coagulopathy but also reduced mortality in a

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Conflict of interest
The authors state that they have no conflict of interest.

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lethal *Escherichia coli* sepsis model in baboons[4]. Similar protection was reported after treatment with either an active site-inactivated FVIIa or the natural anticoagulant tissue factor pathway inhibitor (TFPI)[5,6]. In a baboon model, treatment with an anti-TF monoclonal antibody or an active site-inactivated FVIIa after the establishment of sepsis reduced fibrin deposition and inflammation and attenuated sepsis-induced respiratory and renal failure [7,8]. Inhibition of the TF:FVIIa complex was also protective in a mouse model of cecal ligation and puncture, an endotoxemic mouse model, and a rabbit peritonitis model[9–11]. Further support for the importance of TF in the pathological activation of coagulation came from studies using genetically modified mice. We demonstrated that mice expressing low levels of TF (~ 1% of wild type) had reduced levels of thrombin-antithrombin (TAT), a marker of coagulation, and reduced mortality compared with littermate controls in a model of endotoxemia[12]. Similar protection was observed in endotoxemic mice genetically modified to express low levels of FVII[13]. These data indicate that the extrinsic coagulation pathway plays a major role in the activation of coagulation in endotoxemia and sepsis. However, despite promising results in animals models, blockade of the TF:FVIIa complex with recombinant TFPI had no significant effect on overall mortality in a randomized phase 3 clinical study[14].

TF expression by hematopoietic cells

In general, circulating blood cells do not express TF in healthy individuals[15,16], although very low levels of TF antigen have been detected in a small subset of CD14-positive monocytes [17]. However, many studies have demonstrated that bacterial lipopolysaccharide (LPS) stimulation of human monocytes and monocytic cell lines induces TF expression *in vitro*[17–19]. TF expression was also observed in monocytes from baboons infected with *Escherichia coli* and from septic patients with a *Neisseria meningitidis* infection[20,21]. Furthermore, another study demonstrated that monocytes expressed TF mRNA in a human model of endotoxemia[22]. Our lab and others have shown that either a genetic reduction of TF in hematopoietic cells[12,23], or selective inhibition of TF expression by these cells reduces activation of coagulation by approximately 50% in endotoxemic mice[24]. In addition, using the Cre-LoxP system, we have found that deletion of TF gene in myeloid cells also reduces LPS-induced coagulation in mice[24]. Other studies have reported TF expression by human neutrophils and eosinophils[25,26]. However, more recent studies found that neither neutrophils nor eosinophils express TF but can acquire TF by binding monocyte-derived microparticles (MPs)[27–29]. MPs are small membrane vesicles released from activated or apoptotic cells. This concept was also supported by de Vaard and colleagues who showed that TF-positive granulocytes infiltrating organs do not express TF mRNA in a mouse model of endotoxemia[30]. These studies indicate that within the leukocyte population, monocytes are the predominant cell type that expresses TF and are responsible for activation of coagulation during endotoxemia and sepsis.

In 2001, Engelman and colleagues reported that platelets isolated from collagen-stimulated blood contained functional TF[31]. In a subsequent study they found that activation of platelets results in translocation of TF from α-granules to the cell surface[32]. These provocative observations suggested that platelets are a source of intravascular TF. More recently, other groups showed that quiescent and stimulated platelets express variable levels of TF mRNA and protein[33–35].

In collaboration with Dr. Weyrich’s group, we discovered that human platelets contained TF pre-mRNA and that upon activation this is spliced into mRNA and translated into protein [36]. Interestingly, freshly-isolated platelets from septic patients more frequently express mature TF mRNA and have increased levels of TF protein compared to platelets isolated from healthy controls (Rondina, Schwertz, Weyrich – unpublished data). However, it is likely that some of the TF protein associated with platelets in septic patients is due to the binding of

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leukocyte-derived MPs. Nevertheless, these data suggest that TF expression by platelets may contribute to activation of coagulation during sepsis. It should be noted that other groups have failed to detect any TF protein or TF activity on resting platelets or calcium ionophore-stimulated human platelets[16,37,38]. Therefore, TF expression by human platelets remains highly controversial.

Recently, we investigated the role of TF expression by platelets in the activation of coagulation in a mouse model of endotoxemia. Surprisingly, we failed to detect either TF pre-mRNA or mRNA in unstimulated or activated mouse platelets (Pawlinski, Weyrich, Mackman - unpublished data). Moreover, deletion of the TF gene in megakaryocytes, precursors of platelets, had no effect on plasma TAT levels in endotoxemic mice[24]. These results indicate that there are species-specific differences in platelet TF expression between mice and humans, and that TF expression by platelets does not contribute to activation of coagulation in a mouse model of endotoxemia.

TF expression by non-hematopoietic cells

Many cell types surrounding the vasculature constitutively express TF, including pericytes, adventitial fibroblasts and smooth muscles cells[15,39]. In addition, parenchymal cells in variety of tissues, such as brain, heart, lung, and kidney, express TF[40,41]. Drake and colleagues proposed that TF expressed by these cells forms a hemostatic envelope that limits bleeding when vascular integrity is compromised[15]. However, during endotoxemia and sepsis, there is an increase in vascular permeability that will expose extravascular TF to blood [42]. Furthermore, in endotoxemic and septic animals, TF expression is increased in many organs, such as the brain, lung, kidney, and spleen[30,43–45]. Our recent data demonstrate that selective inhibition of TF expressed by non-hematopoietic cells reduces the activation of coagulation in endotoxemic mice by approximately 50%[24]. This means that hematopoietic and non-hematopoietic cells contribute equally to the generation of TAT at 8 hours in the model. At that point, we do not know the cellular source of TF in the non-hematopoietic cell population that contributes to activation of coagulation. We speculate that TF expression in multiple extravascular cell types in multiple organs contributes to activation of coagulation in endotoxemic mice.

In vitro studies demonstrate that activated endothelial cells (ECs) express TF[46–48]. In contrast, only a limited number of studies were able to demonstrate TF expression by ECs *in vivo*. One study found co-localization of TF and the ECs marker von Willebrand factor within the splenic microvasculature of septic baboons but not in ECs of pulmonary vessels[49]. Another study found TF protein on ECs in endotoxin treated mice and rabbits[44,50]. More recently, TF protein was observed on ECs at branch points of the aorta of septic baboons[51]. TF protein co-localized with fibrin deposition suggesting that it was functional[51]. However, TF present on ECs was restricted to granular structures some of which were also positive for the leukocyte marker P-selectin glycoprotein ligand-1[51]. This suggests that leukocyte-derived MPs may deliver TF to activated ECs *in vivo*. In contrast to these studies, we and others did not detect TF expression by ECs in LPS treated mice, rats, and rabbits[43,45,52,53]. These different results may be caused by the relative sensitivity of the various techniques used to detect TF expression.

One limitation of the above studies was that they all investigated TF expression by ECs but did not analyze the functional contribution of this expression to the activation of coagulation. Recently, we addressed this question using a combination of the Cre-LoxP system and bone marrow transplantation. We found that deletion of the TF gene in ECs had no significant effect on activation of coagulation at 8 hours [24]. One possible explanation for our result is that only small subsets of ECs express TF and/or the expression levels are very low.

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Summary

In summary, TF expression by both hematopoietic and non-hematopoietic cells plays a significant role in the activation of the coagulation cascade during endotoxemia and sepsis. General inhibition of the TF:FVIIa complex reduces coagulation but can also compromise hemostasis, as was observed with the clinical trial using TFPI[14]. We believe that future studies should focus on strategies that selectively inhibit inducible TF expression, for example on monocytes, without affecting TF activity on extravascular cells. This should decrease pathological activation of coagulation and minimize bleeding complications.

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Abbreviation

TF	tissue factor
FVII	factor VII
DIC	disseminated intravascular coagulation
LPS	lipopolysaccharide
TAT	thrombin-antithrombin
TFPI	tissue factor pathway inhibitor
ECs	endothelial cells

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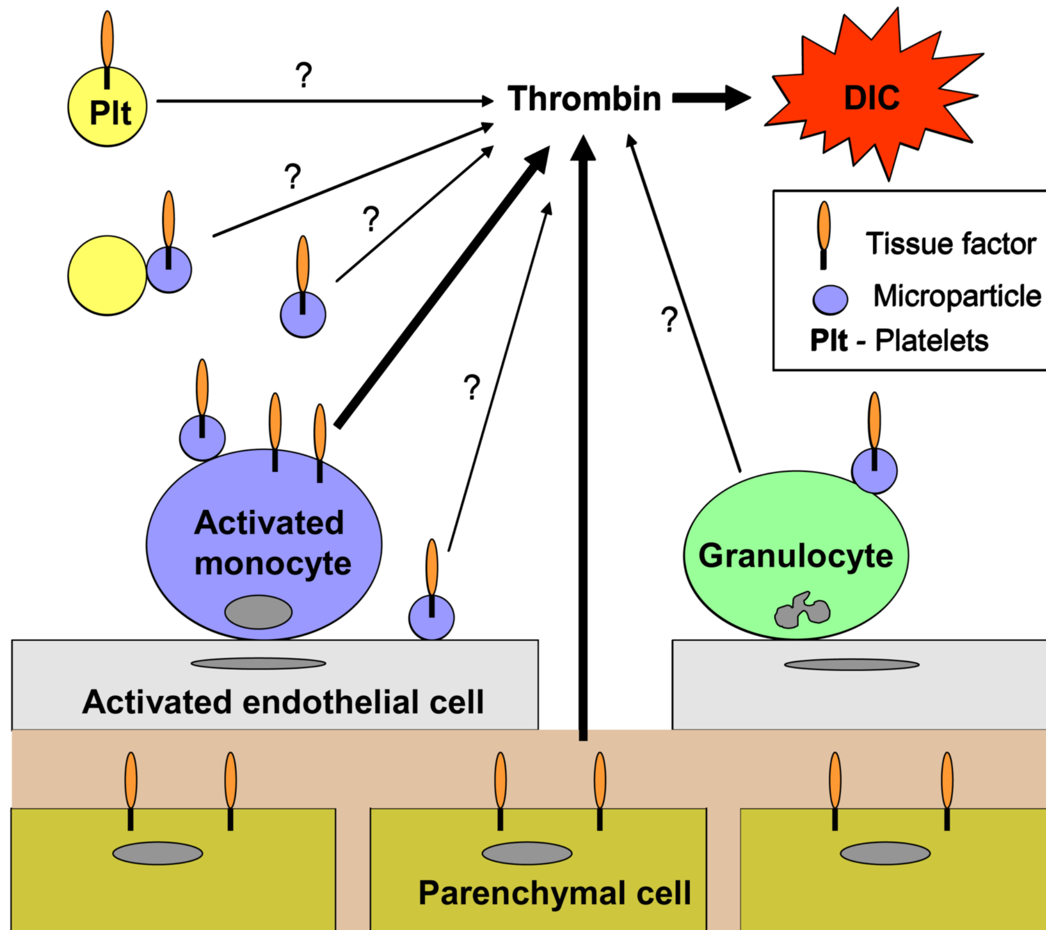

Figure 1. Cellular sources of TF

Activated monocytes and parenchymal cells are two major sources of TF that contribute to activation of coagulation and DIC during sepsis and endotoxemia. In addition, activated monocytes are the main source of TF-positive microparticles which bind to endothelial cells, platelets and granulocytes. The contribution of TF-positive microparticles to the development of DIC has not been determined.