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Mini Review

Sepsis, thrombosis and organ dysfunction

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ABSTRACT

Sepsis is often associated with haemostatic changes ranging from subclinical activation of blood coagulation (hypercoagulability), which may contribute to localized venous thromboembolism, to acute disseminated intravascular coagulation (DIC), characterized by widespread microvascular thrombosis and subsequent consumption of platelets and coagulation proteins, eventually causing bleeding manifestations. The key event underlying this life-threatening complication is the overwhelming inflammatory host response to the infectious agent leading to the overexpression of inflammatory mediators. The latter, along with the microorganism and its derivatives are now believed to drive the major changes responsible for massive thrombin formation and fibrin deposition, namely 1) the aberrant expression of the TF by different cells (especially monocytes-macrophages), 2) the impairment of physiological anticoagulant pathways, orchestrated mainly by dysfunctional endothelial cells (ECs) and 3) the suppression of fibrinolysis due to overproduction of plasminogen activator inhibitor-1 (PAI-1) by ECs and likely also to thrombin-mediated activation of thrombin-activatable fibrinolysis inhibitor (TAFI). The ensuing microvascular thrombosis and ischemia are thought to contribute to tissue injury and multiple organ dysfunction syndrome (MODS). Recent evidence indicates that extracellular nuclear materials released from activated and especially apoptotic or necrotic cells, e.g. High Mobility Group Box-1 (HMGB-1) and histones, are endowed with cell toxicity, proinflammatory and clot-promoting properties and thus, during sepsis, they may represent late mediators that propagate further inflammation, coagulation, cell death and MODS. These insights into the pathogenesis of DIC and MODS may have implications for the development of new therapeutic agents potentially useful for the management of severe sepsis.

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Introduction

Sepsis is almost invariably associated with haemostatic changes ranging from subclinical activation of blood coagulation (hypercoagulability) to systemic clotting activation with massive thrombin and fibrin formation, eventually leading to consumption of platelets and proteins of the haemostatic system (acute disseminated intravascular coagulation, DIC) [1,2]. From a clinical standpoint, septic patients may present with localized thrombotic manifestations, as

Abbreviations: APC, activated protein C; AT, antithrombin; DIC, disseminated intravascular coagulation; ECs, endothelial cells; EPCR, endothelial protein C receptor; HMGB-1, High Mobility Group Box-1; MODS, multiple organ dysfunction syndrome; PAI-1, plasminogen activator inhibitor-1; PC, protein C; PS, protein S; TAFI, thrombin activatable fibrinolysis inhibitor; TM, thrombomodulin; TF, tissue factor; TFPI, tissue factor pathway inhibitor.

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indicated by the observation that they are at increased risk for venous thromboembolism [3,4]. The most common and dramatic clinical feature, however, is widespread thrombosis in the microcirculation of different organs which may importantly contribute to solitary or multiple organ dysfunction (MODS) [1,2]. In fulminant DIC, the consumption of platelets and coagulation proteins will result in simultaneous bleeding of different severity. DIC is classically associated with Gram negative bacterial infections but it can occur in Gram positive sepsis (with a similar incidence) and in systemic infections with other micro-organisms [1,2].

The pathophysiology of sepsis-associated DIC is extremely complex and still extensively investigated. The key event is the systemic inflammatory response to the infectious agent [5]. Following recognition of unique constituents expressed by the causative microorganism and/or of host-derived factors via specific receptors (pattern recognition receptors, PRRs), particularly the Toll-like receptors (TLRs), immune and other host cells (monocytes-macrophages, platelets and endothelial cells among others) synthesize a number of proteins including proinflammatory cytokines. The latter, together with other mediators generated by the inflammatory cascade, including complement activation products [6], act in concert with the microorganisms and/or their derivatives to trigger the coagulation pathways, DIC and organ dysfunction [1,2,7]. Enzymes generated during the clotting cascade, in turn, interact with specific cellular receptors thus eliciting cell responses that amplify the inflammatory reactions [8]. Inflammation can also result in cell apoptosis or necrosis [5] and recent evidence indicates that products released from dead cells, such as nuclear proteins, are able to propagate further inflammation, coagulation, cell death and organ failure [5,9]. This article briefly summarizes current knowledge on the pathogenesis of DIC and MODS, and the ensuing development of potential therapeutics.

Pathogenesis of sepsis-associated thrombus formation

In sepsis the causative agent and the associated inflammatory response drive fibrin formation and deposition by several simultaneously acting mechanisms (Fig. 1), namely 1) up-regulation of procoagulant pathways, 2) down-regulation of physiological anticoagulants and 3) suppression of fibrinolysis [1,2,7].

Up-regulation of procoagulant pathways

The aberrant in vivo expression of TF plays a pivotal role in sepsis-associated blood clotting activation, as indicated by the following observations: 1) the impairment of the TF pathway by various means prevents coagulation abnormalities (including fibrin deposition in target tissues) and lethality in animal models of sepsis or endotoxemia [2,7,10]; 2) the plasma levels of TF are increased in septic patients and generally associated with raised concentrations of markers of clotting activation [2,7,11]. The cellular source of TF in sepsis, however, still remains an open question. In vitro, endothelial cells (ECs) and mononuclear phagocytes have long been known to synthesize TF in response to a wide variety of stimulating agents or conditions that are of pathophysiological importance in sepsis [2,12]. These cells may also exhibit other clot-promoting properties [2], thus providing a surface onto which the clotting pathways are initiated and propagated, eventually leading to fibrin formation in the cell microenvironment. TF expression has been detected also in human neutrophils in response to inflammatory agents [2,13], in eosinophils upon stimulation and subsequent translocation from their specific granules to the cell surface [14], and in activated platelets after de novo synthesis or release from α-granules [2,15,16]. Other studies, however, suggest that these cells do not synthesize TF but acquire it by binding TF-expressing microparticles (MPs) [2,10,17]. MPs are small membrane vesicles released from activated or apoptotic cells that can adhere to the surface of other cells via specific receptors (for instance PSGL-1 on leukocyte-derived MPs and P-selectin on activated platelets or ECs) making the recipient cell capable of triggering and propagating coagulation [2,12].

Although all mentioned cells might contribute to the aberrant in vivo expression of TF, most available studies point to activated monocytes-macrophages as the main triggers of blood coagulation during sepsis (Fig. 1). In animal models of endotoxemia or sepsis, TF expression is increased in important target organs where fibrin deposition often occurs during DIC, namely lung, kidney, liver, spleen and brain and, at cellular level, it is detected mainly in monocytes present in the microcirculation and in macrophages infiltrating the involved tissues [2,10,12,18]. In the same animals, blood monocytes and macrophages of different origin express strong TF activity [2,10,12,18]. In addition, a selective genetic deficiency of TF expression by hematopoietic cells as well as the deletion of TF gene in myeloid cells was found to reduce LPS-induced coagulation, inflammation, and mortality in mice [10,19]. Increased expression of monocyte-macrophage TF has been also documented in healthy volunteers after administration of low-dose endotoxin [20], in septic or endotoxemic patients, in whom TF was associated with clotting activation, MODS and lethal outcome, and in patients with peritonitis or acute respiratory distress syndrome [2,7,12,18]. Further support for a prominent role of monocytes-macrophages comes from studies on MPs. In endotoxemic mice, levels of MP TF activity were correlated with coagulation activation [21]. In addition, increased numbers of circulating TF-positive MPs of monocyte origin have been detected in patients with meningococcal sepsis and in human low-dose endotoxemia [2,7,22]. Surprisingly, and in contrast with the abundant in vitro evidence, ECs were negative for TF in most animal studies, with very few exceptions [2,10,17,18]. Moreover, the deletion of the TF gene in ECs had no significant effect on clotting activation in endotoxemic mice [10,19], clearly ruling out a major involvement

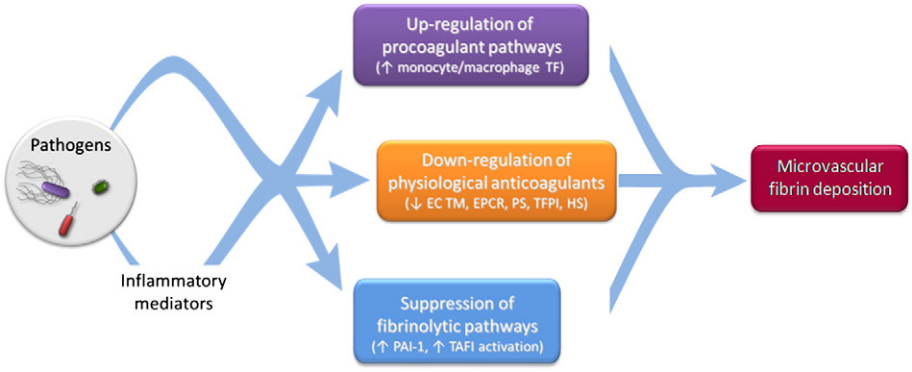

Fig. 1. Mechanisms contributing to thrombin formation and fibrin deposition in the microcirculation (see text for details). TF, tissue factor; EC, endothelial cell; TM, thrombomodulin; EPCR, endothelial protein C receptor; PS, protein S; TFPI, tissue factor pathway inhibitor; HS, heparan sulphate; PAI-1, plasminogen activator inhibitor-1; TAFI, thrombin activatable fibrinolysis inhibitor.