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Crosstalk between the coagulation and complement systems in sepsis

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ABSTRACT

Sepsis is a potent activator of the hemostatic and complement systems. While local activation of these proteolytic cascades contributes to the host defense, their uncontrolled systemic activation has major tissue damaging effects that lead to multiple organ failure and death. We have extensively studied the activation of complement and coagulation cascades in experimental sepsis using baboons challenged with live bacteria, such as Gram-negative *Escherichia coli* or Gram-positive *Staphylococcus aureus* and *Bacillus anthracis*, or with the bacterial product peptidoglycan. We observed that these challenges rapidly induce disseminated intravascular coagulation and robust complement activation. We applied a potent C3 convertase inhibitor, compstatin, which prevented sepsis-induced complement activation, reduced thrombocytopenia, decreased the coagulopathic responses, and preserving the endothelial anticoagulant properties. Overall, our work demonstrates that live bacteria and bacterial products activate the complement and coagulation cascades, and that blocking formation of complement activation products, especially during the organ failure stage of severe sepsis could be a potentially important therapeutic strategy.

Introduction

Sepsis is multistage, multi-factorial disease and a major cause of morbidity and mortality worldwide [1,2]. Sepsis progression results in the aberrant breakdown of the blood/tissue barrier due to an exaggerated and systemic host response to bacterial pathogen-associated molecular patterns (PAMPs) [2]. The excessive activation of inflammation, complement and coagulation systems damage the host's own tissues and organs leading to multiple organ failure and death [3]. Moreover, sepsis survivors can have life-long impairments, ranging from limb amputations to diffuse organ fibrosis [4] that affect the quality of life and increase the risk of death from subsequent challenges. Despite the clinical importance of the disease and extensive research, no specific treatment is available for sepsis.

In this review we present recent advancements in the field, with particular focus on the pathophysiology of sepsis and the inter-talk between complement, coagulation and innate immunity during sepsis progression, as revealed by the experimental models in baboons.

Models of Sepsis Progression in Baboons

As illustrated in Fig. 1, live bacteria or bacterial-derived PAMPs, such as lipopolysaccharide (LPS or endotoxin) from Gram negative (G-) or peptidoglycan (PGN) from Gram positive (G+) bacteria, bind pattern-recognition receptors (PRR) such as Toll-like receptor (TLR) 4, or nucleotide oligomerization domain (NOD) receptors [5], respectively. Recognition of PAMPs by PRRs triggers a cascade of cellular signals that activate the transcription factor nuclear factor kappa B (NFkB) leading to rapid and massive production of inflammatory mediators and induction of procoagulant activities such as tissue factor expression [6]. Non-human primate models of *E. coli* sepsis developed by our group demonstrated that the events controlling sepsis progression are spatially and temporarily defined and have specific inducers [2]. Early events are direct intravascular responses to the PAMPs of invading pathogens, while late events are associated with extravascular ischemia-reperfusion (IR) injury and oxidative stress (OS) [2].

Activation of Coagulation in Sepsis

Like inflammation, activation of blood clotting cascade during sepsis is a host-defense mechanism that facilitate the containment and destruction of pathogens to protect against bacterial spreading within the body.

Abbreviations: APTT, activated partial thromboplastin time; C3, complement protein C3; C3a, complement protein C3a; C4a, complement protein C4a; C5a, complement protein C5a; C5b-9, terminal complement complex; E. coli, Escherichia coli; DIC, disseminated intravascular coagulation; G-, Gram negative bacteria; G+, Gram positive bacteria; IR, ischemia-reperfusion; LPS, lipopolysaccharide; NFkB, nuclear factor kappa B; NOD, nucleotide oligomerization domain; OS, oxidative stress; PRR, pattern-recognition receptors; PAMPs, pathogen-associated molecular patterns; PGN, peptidoglycan; PS, phosphatidylserine; TF, tissue factor; TFPI, tissue factor pathway inhibitor; TLR, Toll-like receptor.

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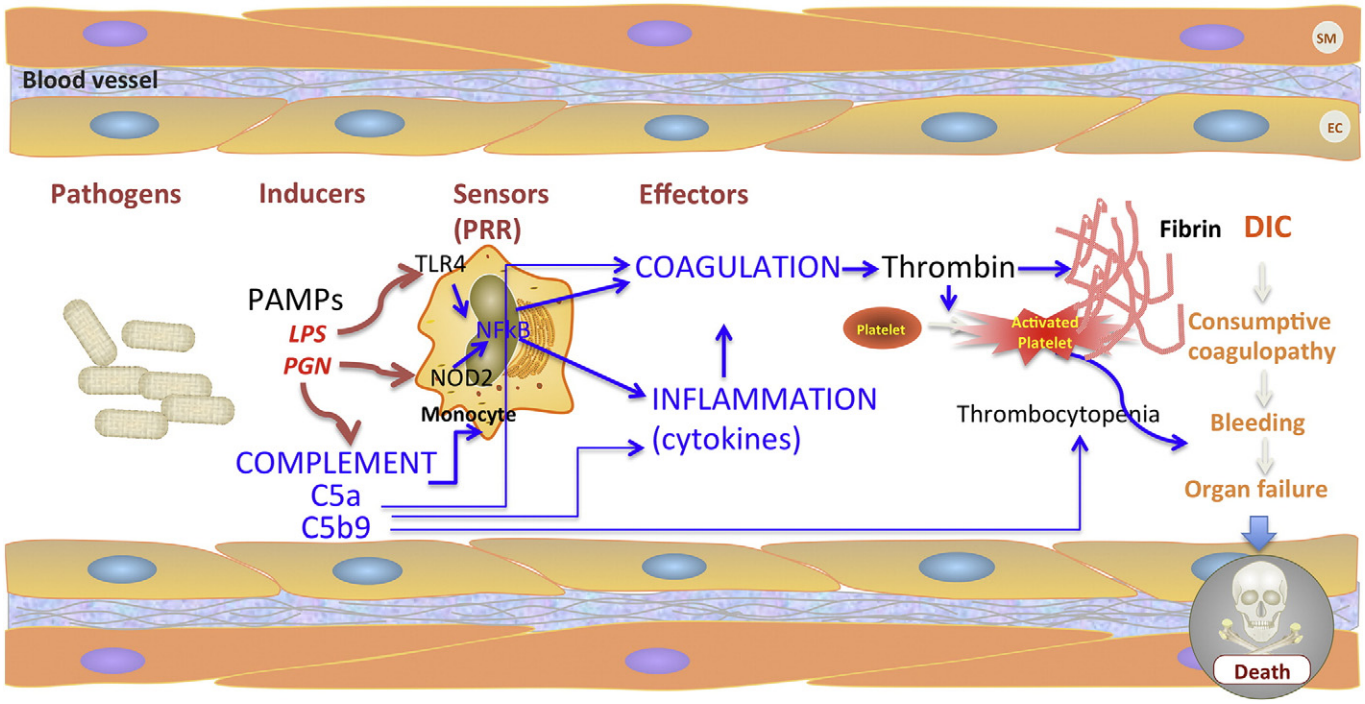

Fig. 1. Interactions between inflammation, coagulation and complement activation during sepsis progression.

Inflammation and coagulation are tightly inter-connected. Uncontrolled inflammation can promote disseminated intravascular coagulopathy (DIC), a central event in the pathophysiology of sepsis and probably the most important marker of poor prognosis. DIC is characterized by massive thrombin production and platelet activation/consumption, coupled with impaired fibrinolysis and microvascular thrombosis.

Sepsis-induced DIC is driven by: (i) tissue factor (TF)-mediated thrombin generation [6]; (ii) depression of natural anticoagulant mechanisms (antithrombin, protein C and TFPI) and impaired fibrinolysis which cannot balance the overwhelming procoagulant activity [7]; (iii) activation of the complement system, that can further amplify the inflammation and coagulation responses and promote tissue damage [8].

Induction of Procoagulant Factors

There are strong evidences that coagulation in sepsis is primarily TF-driven [6]. TF activates coagulation via the extrinsic pathway, involving factor VIIa. The TF-VIIa complex activates thrombin, which cleaves fibrinogen to fibrin while simultaneously causing platelet aggregation. The actual source of the TF is not fully established. While TF expression by monocytes is well established, TF was also detected on polymorphonuclear leukocytes, platelets and endothelial cells, although is not clear if is synthesized or transferred to these cells via monocyte-derived microparticles [6]. Focal TF increases at branches of large vessels and within the subendothelial space and this is associated with fibrin deposition and increased endothelial permeability [9]. Targeting of the extrinsic pathway with monoclonal antibodies or inhibitors specifically directed against TF [10] or factor VIIa activity [11] prevented the occurrence of DIC organ failure and mortality in baboons that were infused with *E. coli* [12].

Intrinsic pathway of coagulation, also known as contact activation or kallikrein/kinin system is located at the interface between coagulation, fibrinolysis and complement activation. Moreover, contact activation leads to the release of Bradykinin, a highly potent proinflammatory, vasoactive peptide. Systemic activation of the contact system was reported both in animal models [13] and patients suffering from sepsis. Activation of this pathway may contribute not only to DIC but also to other serious complications such as hypotension and vascular leakage [13]. Inhibition of factor XI activation was reported to attenuate inflammation and coagulopathy and to improve survival in a mouse model of polymicrobial sepsis [14]. Otherwise, upstream inhibition at factor XII level did not prevent DIC but alleviated sepsis induced hemodynamic instability and hypotension in the baboon model of E. coli sepsis [15]. These discordances may reflect differences in the animal model and/or bacterial challenge.

Depression of Anticoagulant Mechanisms

Several anticoagulant proteins, including Protein C, antithrombin, thrombomodulin and TFPI are markedly decreased in septic baboons and in patients with DIC [7]. This reduction is caused by decreased synthesis, increased consumption, degradation by proteases, such as plasmin [16,17], supporting a role for plasmin in proteolytical degradation of TFPI during sepsis. Moreover, acute thrombin generation can contribute to the depletion of the endothelial pool of TFPI [18].

While most of functionally relevant TFPI is associated with endothelial cells and platelets, pharmacologic doses of TFPI delivered in plasma, prevented mortality, suggesting that high concentrations of TFPI can control TF-mediated coagulation during systemic inflammation in baboons [19].

The damaging effects of DIC prompted the use of anticoagulants as sepsis therapy. This had mixed results because of the duality of DIC as both clotting and bleeding disorder, where the consumption of clotting factors and platelets can lead to severe bleeding that also contribute to organ failure and death. Anticoagulant therapies have failed in clinical trials, because of bleeding adverse effects [15].

Activation of Complement in Sepsis

Similar to coagulation, complement is a critical component of the innate immune defense against pathogens but uncontrolled complement activation can contribute to the pathology of sepsis [20]. The immunoglobulin-initiated classical pathway or the mannose binding lectin-initiated pathway converge on C3 activation before assembly of the C5b-9 terminal attack complex. The small activation fragments that are released during the activation of complement, C3a and C5a (also called anaphylatoxins) have potent proinflammatory effect by