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The relationship between inflammation and the coagulation system

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Summary

Inflammation and coagulation play pivotal roles in host defence. As phylogenetically old responses, there is extensive cross-talk between inflammation and coagulation in enabling an adequate immune response against potentially injurious stimuli. Immune cells are important in the initiation of coagulation pathways, while various inflammatory mediators are capable of altering haemostasis. Vice versa, coagulation proteases have significant immunomodulatory effects. Understanding the mechanisms involved in the cross-talk between inflammation and coagulation may yield new therapeutic strategies for human diseases.

Key words: innate immunity; coagulation; fibrinolysis; infection; inflammation

Introduction

Severe infections are characterised by an acute inflammatory response, and are almost invariably accompanied by alterations of the coagulation system [1]. The activation of both the immune system and the coagulation system are not merely associated in time, but there has been extensive cross-talk between the two systems throughout vertebrate evolution [2].

The primary goal of the immune system obviously is host defence. Upon injury by a microorganism, immune cells are recruited and proinflammatory cytokines are generated. Also coagulation is almost immediately activated, directed at confinement and sequestration of the harmful intruder. While localised inflammation and clotting clearly have host-protective functions, it is considered disadvantageous when the inflammatory response is not limited to the primary site of injury and spreads through the body. The detrimental effects of generalised clotting are best exemplified in the clinical syndrome of sepsis: the systemic inflammatory response and accompanying excessive coagulation activation lead to consumption of clotting factors and widespread depositions of fibrin, causing diffuse endothelial damage, multiple organ dysfunction, and eventually death [1]. In this review, we will discuss the bi-directional relationship between inflammation and coagulation.

Inflammation induces activation of coagulation

In the activation of coagulation in disease states, tissue factor (TF) plays a central role. Under normal conditions, only small amounts of TF reach circulating blood, but in inflammatory states monocytes can express TF on their surface [3]. Also microparticles from activated platelets and endothelial cells may serve as additional sources of TF [4], but their significance in vivo is under ongoing debate [5–8]. TF binds and activates factor VII (FVIIa), out of which the coagulation network is activated and thrombin is generated. Thrombin converts fibrinogen into fibrin and induces platelet aggregation, forming a clot. In models of experimental sepsis or endotoxaemia, inhibition of the TF-FVIIa complex was repeatedly shown to limit coagulopathy and lethality [9–11], while mice expressing low levels of TF on haematopoietic cells were less likely to show excessive coagulation

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after endotoxin-challenge, resulting in less mortality [12].

Proinflammatory cytokines are important mediators of activation of coagulation. Infusion of tumour necrosis factor (TNF)-α into healthy human volunteers induced not only signs of a systemic inflammatory response, but also activation of coagulation as indicated by an increase in plasma concentrations of the prothrombin fragment F1+2 [13]. However, blocking TNF-α with monoclonal antibodies did not neutralise coagulation activation during endotoxaemia in chimpanzees [14]. Rather, blocking interleukin (IL)-6 attenuated activation of coagulation in the same model of endotoxaemia, both systemically and locally in the bronchoalveolar compartment [15, 16]. This suggested that IL-6 was the most important mediator in inflammation-induced coagulation. Hence, the proinflammatory cytokines IL-6 and TNF-α establish a procoagulant shift in the haemostatic balance, promoting fibrin generation in severe inflammatory states, both systemically and locally (figure 1).

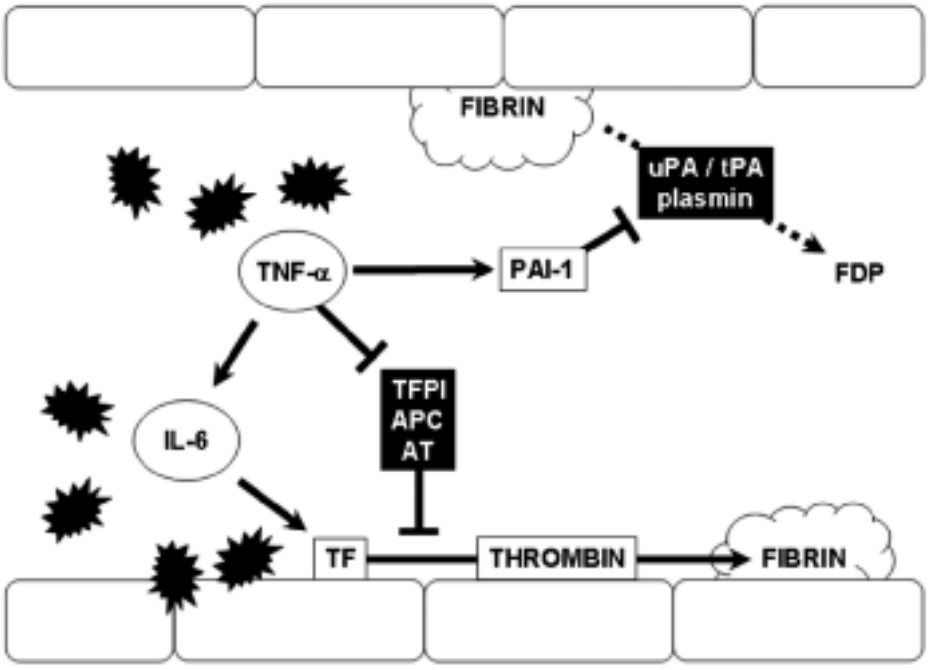

Figure 1

Inflammation-induced coagulation Upon intrusion by a microorganism, tissue factor (TF) up-regulation is induced on mononuclear cells (not shown in figure). Also, within hours the immune system produces a number of cytokines, such as tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6). IL-6 induces up-regulation of TF on the cell surface, causing thrombin-mediated fibrin depositions. The activation of coagulation is regulated by the natural inhibitors of coagulation, ie, tissue factor pathway inhibitor (TFPI), activated protein C (APC), and antithrombin (AT). However, TNF-α decreases the expression of these inhibitors. Finally, fibrinolysis is inhibited (FDP, fibrin degradation products), because up-regulation of plasminogen activator type 1 (PAI-1) suppresses plasminogen activation (urokinase-type and tissue-type plasminogen activators, uPA and tPA).

Inflammation-induced coagulation is not counterbalanced

There are other mechanisms promoting inflammation-induced clotting, ie, a relative insufficiency of the natural anticoagulant systems, and a simultaneous suppression of the fibrinolytic system. Once again, proinflammatory cytokines are – at least partially – responsible for these effects (figure 1).

Mechanisms that regulate the coagulation system under normal conditions involve natural inhibitors of coagulation, including antithrombin, activated protein C (APC), and tissue factor pathway inhibitor (TFPI). In general, they interfere with the activation of coagulation, but on different levels: TFPI complexes with factor Xa and inhibits TF-FVIIa; APC inactivates factors Va and VIIIa, thereby abrogating thrombin generation; antithrombin neutralises many enzymes in the coagulation network, including thrombin, factors Xa, and IXa. In patients with sepsis, systemic levels of antithrombin and protein C are decreased, because of increased consumption, impaired synthesis, and degradation [17, 18]. In addition, thrombomodulin – the pivotal mediator of thrombin-induced protein C activation – is down-regulated at the endothelial surface by proinflammatory cytokines, such as TNF-α and IL-1β, resulting in dysfunction of the protein C system [19–22]. The importance of the protein C pathway has been demonstrated in numerous preclinical studies. Blockade of the protein C system resulted in an increased mortality after a Gram-negative challenge in baboons [23, 24]. Conversely, infusion of APC resulted in improved survival after a lethal Gram-negative challenge [25], while a 96-hour infusion of recombinant human (rh-)APC was shown to improve survival in patients with severe sepsis [26]. TFPI also plays a relevant role in coagulopathy. TFPI depletion sensitised rabbits to diffuse intravascular coagulation induced by TF-infusion [27]. Moreover, TFPI infusion protected against mortality in baboons infused with endotoxin or Escherichia coli [28], and in mice and rabbits with abdominal sepsis [29, 30]. Most recently, Chen et al. generated transgenic mice expressing hirudin and human TFPI at the surface of activated endothelium, eg, after endotoxin challenge [31]. These

mice were protected against coagulopathy during endotoxaemia, and the authors speculated that patients with sepsis would benefit from endothelium-targeted anticoagulant treatment [31]. Finally, rh-TFPI effectively and dose-dependently attenuated the endotoxin-induced coagulation activation in humans [32]. However, treatment with rh-TFPI failed to improve patient outcome in human sepsis [33]. Perhaps the applied dose was sufficient for anticoagulant effects, but not for significant anti-inflammatory effects [34].

Inhibition of the fibrinolytic system is another event that facilitates fibrin deposition in the presence of proinflammatory cytokines. Clearly, the procoagulant state caused by TNF-α is accompanied by inhibition of fibrinolysis [13, 35]. In the acute inflammatory response fibrinolysis is immediately increased by plasminogen activators, which are released from the endothelium. Subsequently plasminogen activation is hampered by a sustained increase in plasminogen activator inhibitor type-1 (PAI-1) [35]. Both TNF-α and IL-1β have been found to exert antifibrinolytic effects by stimulating the release of PAI-1, and by reducing the release of tissue-type plasminogen activator [36, 37].

To summarise the effects of severe inflammation on haemostasis, high levels of circulating proinflammatory cytokines cause massive systemic activation of coagulation while seriously inhibiting both fibrinolysis and natural anticoagulation.

Coagulation proteases modulate inflammation

Activation of coagulation promotes an accelerated inflammatory response via various mechanisms. In particular, coagulation proteases interact with protease-activated receptors (PARs), which are believed to play a key role in translating coagulation products into inflammatory signals [38]. PARs are transmembrane proteins that are expressed on the surface of mononuclear cells and endothelial cells among others, and currently 4 types (PAR-1 through -4) have been identified [38]. Upon proteolytic cleavage by an activated coagulation factor, a PAR is able to activate itself by the exposed neoamino terminus.

Thrombin exerts its proinflammatory effects mainly through the PAR-1, but also has high affinity for PAR-3 and -4 [38]. Thrombin thereby induces up-regulation of various proinflammatory cytokines in vitro, including monocyte chemotactic protein-1, IL-6, IL-8, and macrophage migration inhibitory factor [39–43]. In addition, acting through nuclear factor-κB, it enhances expression of adhesion molecules, promoting leukocyte adhesion [44]. Similar effects have been described for factor Xa and the TF-VIIa complex [45, 46]. Binding of the latter to PAR-2 also results in up-regulation of inflammatory responses in macrophages and was shown to affect neutrophil infiltration and proinflammatory cytokines TNF-α and IL-1β expression [47]. In vivo evidence for the role of coagulation-induced inflammation comes from experiments in which rh-FVIIa induced a 3- to 4-fold rise in plasma levels of IL-6 and IL-8 in healthy human subjects [48].

Taken together, a number of coagulation proteases exert proinflammatory effects on cells and through cell-cell interactions, creating an amplification route for even more inflammation and coagulation.

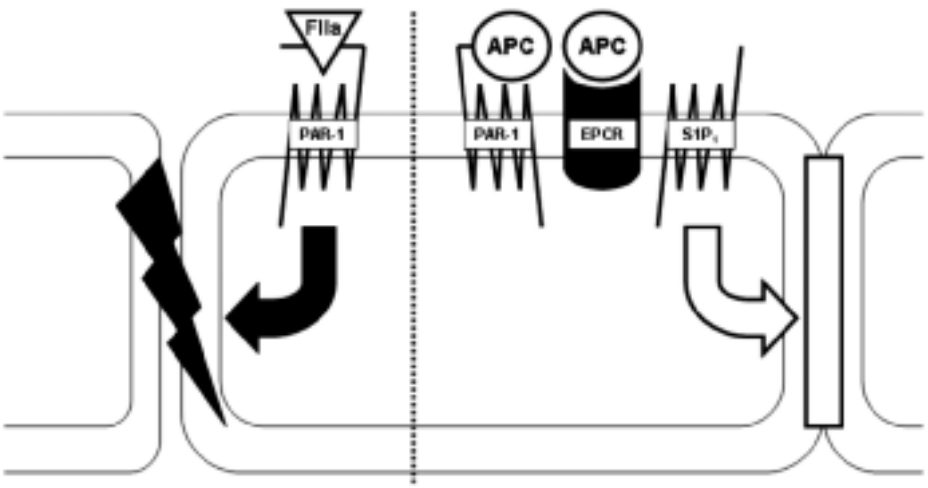

Figure 2

Proposed mechanisms of protease-activated receptor (PAR)-1 mediated regulation of vascular integrity. Thrombin (FIIa) disrupts the vascular barrier by PAR-1 cleavage (left). Activated protein C (APC) binds to the endothelial protein C receptor (EPCR) and has barrier protective effects either by direct sphingosine 1-phosphate receptor-1 (S1P1) cross-activation or indirectly via PAR-1 (right). Models are as proposed in [55, 56].

The protein C pathway and the effects on innate immunity

Recently, the effects of APC on PARs have received much attention. Part of it has been inspired by the human sepsis trial in which rh-APC was shown to reduce mortality [26]; it was clear that, although sepsis patients with more severe coagulation abnormalities benefited most from APC therapy [49], the beneficial effects of APC were not solely dependent on its anticoagulant activity [50]. The most consistent finding from preclinical studies is the effect of APC on leukocyte adhesion and extravasation. In animal models of endotoxaemia APC was shown to reduce leukocyte extravasation and tissue accumulation [51–54]. Nick et al. reproduced these finding in human volunteers who underwent bronchial instillation of endotoxin: intravenous infusion with APC prevented leukocyte infiltration into the lungs [53], and largely preserved normal bronchoalveolar haemostasis [55].

To date, several cellular mechanisms have been proposed to clarify these in vivo effects. APC exerts many anti-inflammatory effects in vitro, eg, inhibition TNF-α production by monocytes/macrophages, suppression of NF-κB expression, inhibition of cytokine signalling, interference with cytokine-induced up-regulation of cell surface leukocyte adhesion molecules and genes related to inflammation [56–59]. Riewald et al. proposed that PAR-1 was a major target of APC signalling [60], but it remained unclear how the same signalling receptor could possess both pro- and anti-inflammatory effects, dependent on the protease involved. New studies suggest that APC bound to endothelial protein C receptor may exert protective effects on the vascular barrier via sphingosine 1-phosphate receptor-1 cross-activation; either directly or via PAR-1 [61, 62]. However, the in vivo relevance of APC-mediated PAR-1 activation has been challenged [63], since the described cellular effects of APC in vitro are at concentrations much higher than achieved during the treatment of severe sepsis. Compared to thrombin, approximately a thousand- to ten thousand-fold higher concentrations of APC are needed for PAR-1 activation [64]. Indeed, the anti-inflammatory effects of rh-APC in patients with sepsis were shown to be very modest [26, 65].

Conclusion

Inflammation and coagulation have reciprocal amplifying effects, potentially constituting an environment that is highly proinflammatory and procoagulant in severe disease states. Elucidating the mechanisms of cross-talk between coagulation and inflammation increases our understanding of the pathological and pathophysiological events of severe clinical diseases, and may yield new therapeutic targets in the near future.

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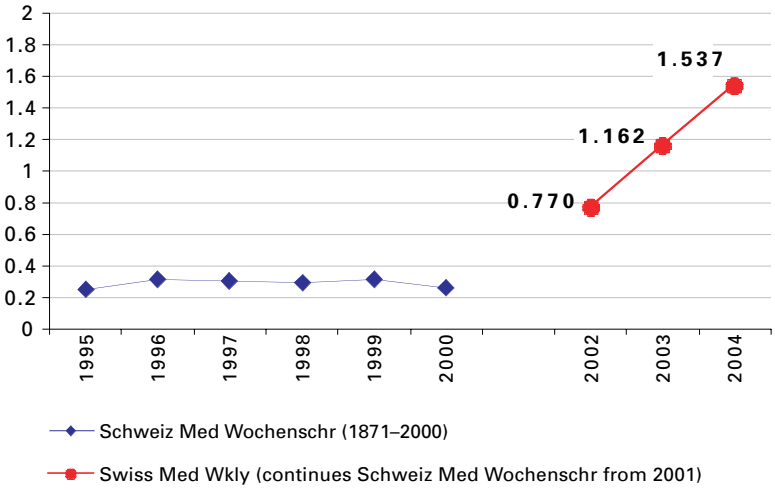

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