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The coagulation system and its function in early immune defense

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Abstract

Blood coagulation has a Janus-faced role in infectious diseases. When systemically activated it can cause serious complications associated with high morbidity and mortality. However, coagulation is also part of the innate immune system and its local activation has been found to play an important role in the early host response to infection. Though the latter aspect has been less investigated, phylogenetic studies have shown that many factors involved in coagulation have ancestral origins which are often combined with anti-microbial features. This review gives a general overview about the most recent advances in this area of research also referred to as immunothrombosis.

Introduction

Blood clotting is initiated only seconds after vascular injury which makes it one of the fastest tissue repair systems in our body (1). Its main purpose, sealing an injured vessel, is accomplished by an aggregation of platelets at the site of the lesion. This will then lead to a loose platelet plug, which is further stabilized by the formation of a fibrin network. Both events, also known as primary and secondary hemostasis, not only help prevent the efflux of blood cells and plasma proteins into the surrounding tissue, but also trigger wound healing and tissue regeneration processes. As bleeding sites are potential ports of entry for microorganisms, coagulation is also one of the first humoral regulatory systems that encounters an intruder. It therefore seems plausible that during activation of coagulation, immune defense machineries are also alerted and activated. This in turn should help diminish the risk of systemic microbial invasion. In fact, mammals have established a manifold arsenal of defense mechanisms which are mobilized when coagulation is activated. These include for instance the release of antimicrobial peptides (AMPs) from platelets (2) or their generation during clot formation (3). In addition, cellular responses are triggered; for example an intact platelet-fibrinogen plug can provide an active surface that allows the recruitment, attachment, and activation of phagocytizing cells (4) and many coagulation factors are able to induce pro- and anti-inflammatory reactions by activating so-called protease activated receptors (PAR) on immune cells (5). These findings have lately attracted considerable attention and has led to a novel area of research which is now referred to as "*immunothrombosis*" in the literature (6). The present review aims to provide an overview of the role of the coagulation system in the early immune response to bacterial infection (Figure 1).

Hemostasis and inflammation

Hemostasis and inflammation are tightly interwoven and can regulate each other in a concert action when activated during infection (7). The efficacy to eradicate the invading pathogen is to a great deal dependent on the amplitude of the coagulative and inflammatory responses of the host. Both systems are normally down-regulated under non-infectious conditions. However, as soon as an invading pathogen is sensed, they can become activated and start initiating immune reactions and wound healing processes. In order to guarantee an efficient elimination of the pathogen, the amplitude of these responses has to be in a physiologically relevant range. Under

certain conditions, host control mechanisms can fail and systemic activation of coagulation and inflammatory cascades can reach pathological dimensions. These complications are combined with high morbidity and mortality and are almost impossible to treat (8).

Extrinsic pathway of coagulation

Tissue factor (TF), also referred to as CD142 or thromboplastin, is a membrane-spanning glycoprotein and the principal activator of the extrinsic pathway of coagulation. The protein is constitutively expressed on many extravascular cells, such as fibroblasts, pericytes, and epithelial cells, while it is found at low levels, or in an encrypted form, on cells which are in constant contact with plasma proteins (9). Some cell types such as monocytes and endothelial cells can up-regulate TF on their surface under inflammatory conditions (10). Apart from its essential role in activating the coagulation cascade, TF shares structural homology with class II cytokine receptors (11) and can evoke a number of inflammatory reactions (12). It was as early as 1995 when it was reported for the first time that binding of factor VII to TF triggers the mobilization of cytosolic calcium in many cell types (13). Today it is known that TF can signal via a PAR-dependent and independent pathway involving two completely different modes of action (14). The PAR-dependent pathway engages TF as a cofactor and docking protein that is required for interaction of factors VII and X with PAR2 (15). The PAR-independent pathway on the other hand is activated by an alternatively spliced form of TF which interacts with integrins and leads to an activation of members of the mitogen activated protein kinase family (16). Both pathways have been shown to evoke inflammatory responses such as the release of cytokines, chemokines, and adhesion factors (17, 18). Activation of TF can be part of the host defense to infection and a protective role for TF in infectious disease models was, for instance, described by Deyan Luo and co-workers who published that mice with low tissue factor activity succumb to yersinios (19). Although these findings point to a critical role of TF in the host defense against *Yersinia enterocolitica*, TF is not an interesting target for drug development as its systemic activation bears the risk of life-threatening complications, as discussed later.

In addition to TF, its regulators are also involved in the early immune defense. Papareddy and colleagues, for example, reported in 2010 that the carboxy-terminal part of tissue factor pathway inhibitor 1 (TFPI-1) has antimicrobial properties that can

kill a number of pathogens including Gram negative (*Escherichia coli* and *Pseudomonas aeruginosa*) and Gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*), as well as a number of fungal species (*Candida albicans* and *Candida parapsilosis*) (20). The same authors reported that tissue pathway inhibitor 2 (TFPI-2), a homologue of TFPI-1, also explores antibacterial activity upon proteolytic processing (21). TFPI-2 is a weak TF inhibitor, but it interacts with a wide range of other coagulation factors and is up-regulated under inflammatory conditions (22, 23).

Intrinsic pathway of coagulation

In 2003, Esmon and Opal stated that the "pattern recognition molecules of the innate immune system function in a manner that is remarkably similar to that of contact factors of the intrinsic clotting system" (24). Indeed during the last two decades, the list of bacterial pathogens that are recognized by the contact system is steadily increasing and it includes all types of microorganisms (25). Contact activation at the bacterial surface leads to the generation of bradykinin that is released from plasma kallikrein-processed high-molecular weight kininogen. Bradykinin can be further cleaved to des-Arg^9-bradykinin (26). Both kinins are potent inflammatory mediators with specific pharmacological profiles because they signal via distinct receptors. Notably, the tissue distribution and physiological characteristics of the two receptors show marked differences (27). While bradykinin binds to B2R, a receptor that is constitutively expressed and involved in acute inflammatory reactions, des-Arg^9-bradykinin has higher affinity to B1R. In contrast to B2R, B1R is inducible and has been found to evoke chronic inflammatory responses (27). B2R and B1R have been implicated in the early defense against microorganisms. Monteiro and co-workers for instance, employed a *Trypanosoma cruzi* infection model to show that the cooperative activation of B2R and Toll-like receptor 2 is responsible for an interferon-γ response in dendritic cells. These findings allowed the authors to conclude that bradykinin is capable of linking innate and adaptive immune responses (28). Passos and colleagues on the other hand, reported that LPS-induced up-regulation of B1R leads to a NF-κB mediated cytokine response followed by the recruitment of neutrophils (29). Together these findings suggest that both kinins play an important role at different stages of the host response to infection.

When activated by bacteria such as *Streptococcus pyogenes*, contact activation leads

to the release of kininogen-derived AMPs with a broad activity (3). Other studies with *Escherichia coli, Pseudomonas aeruginosa,* and *Enterococcus faecalis* have shown that even more AMPs are generated when kininogens are further processed with neutrophil elastase (30). A release of AMP from the other three contact factors (plasma kallikrein, factor XI, and factor XII, respectively) has not been described. It has been proposed that the antimicrobial activity of kininogens has resulted in a different evolutionary pressure on kininogens compared to the other contact factors. Cagliani and colleagues recently published a phylogenetic analysis showing no consistent evidence of adaptive evolution for plasma kallikrein, factor XI, and factor XII, while strong signatures of diversifying positive selection were detected for kininogens (31). Based on their findings, the authors concluded that kininogens have been a target of long-lasting and strong selective pressure, suggesting that kininogens play a central role in the modulation of the innate immune response (31).

The common pathway of coagulation

The final step in the clotting cascade starts with the processing of fibrinogen by factor X-activated thrombin. This will eventually lead to the formation of a fibrin clot which is further stabilized by the action of factor XIII (32). Concomitantly, thrombin activates protein C and thereby initiates repression of hemostasis (33). As mentioned before, PAR receptors are an important link between coagulation and inflammation. While factor X targets PAR1 and PAR2, thrombin can also activate PAR3. In both cases, activation triggers pro-inflammatory reactions such as the inductions of IL-6, IL-8, TGF-β, and monocyte chemoattractant protein-1 (34). The activation of PAR1 by activated protein C (APC) is more complicated and requires a docking protein, endothelial protein C receptor or EPCR. In contrast to PAR1 activation by factor X or thrombin, APC evokes anti-inflammatory reactions, including for instance inhibition of leukocyte adhesion and maintaining endothelial barrier function (35). The molecular mechanisms underlying different PAR1 signaling are not completely understood but several modes of actions have been proposed as summarized by a review article from Versteeg and colleagues (1). In addition to PAR1 activation, a recent study has shown that APC cleaves and neutralizes extracellular histones in a murine infection model thereby preventing lethality in these animals (36). Notably, APC has been used as a treatment in patients suffering from severe infectious

diseases, but due to lack of efficiency it was withdrawn from the market in 2011 (37). Many coagulation factors, including factor X and thrombin, contain a sequence at their carboxyterminal region of the catalytic domain that explores antimicrobial activity when generated by proteolytic processing (38). In the case of thrombin, such a peptide was found to be released under *in vitro* and *in vivo* conditions (20) and when injected into mice the peptide was able to modulate inflammatory reactions and protect animals from endotoxin-induced shock (39). These findings suggest that coagulation factors, such as prothrombin, have more functions that are of importance in the host response to infection. Notably, phylogenetic analyses revealed that vertebrate coagulation factors, including factor X and thrombin, share ancestry with complement proteinases. It has therefore been concluded that blood clotting has emerged as a byproduct of the innate immune system (40). It is worth noting that fibrinogen-like proteins have also been described to have an important role in ancestral immunity. Proteins containing fibrinogen motifs have been found in numerous invertebrate organisms. While these proteins play a critical role in the immune response to infection, they are not involved in blood clotting. A role for fibrinogen in hemostasis has occurred evolutionary only recently, with the first description being in deuterostomes (41). In vertebrates, processing of fibrinogen leads to a number of immune reactions such as the release of antimicrobial peptides, chemotactic responses triggered by fibrinogen-derived peptides, and neutrophil recruitment and adhesion (4, 42, 43). Apart from triggering these immune reactions, fibrinogen when processed to fibrin, can also act as a physical barrier that entraps bacteria within a formed clot. Additional crosslinking of the captured microorganisms by the action of coagulation factor XIII, a transglutaminase, helps to immobilize the pathogen in the clot and prevent its further dissemination (44).

Procoagulant microparticles

Microparticles (MPs, also referred to as microvesicles or ectosomes) are vesicles measuring 0.1 to 2 μm that are shed from the plasma membrane of multiple cell types upon activation or apoptosis by a process that involves reorganization of the membrane lipid composition and the translocation of phosphatidylserine to the outer leaflet (45, 46). MPs lack a nucleus and express antigens of the cell from which they are derived, allowing investigations of the function of cell-specific MPs in various disease states. MPs represent a circulating pool of biologically active molecules,

containing proteins, messenger and microRNA's, as well as lipids; the MP content may vary depending on cellular origin and disease state. Apart from exerting a large variety of proinflammatory and procoagulant properties, they can also function to transfer biological information between cells and organs. MPs can be detected at low levels in the circulation of healthy individuals, predominantly originating from platelets, where they induce low grade thrombin generation (47). Upon disruption of the integrity of the vascular endothelial barrier, platelet-derived MPs are important for primary hemostasis. The outer surface of MPs is enriched in phosphatidylserine, which provides a catalytic surface for the assembly of contact factors and vitamin K-dependent enzyme complexes of the coagulation system (factors VII, IX, X and thrombin) (45, 46, 48). While intact platelets are essential for triggering blood coagulation, platelet MPs offer an additional phospholipid platform that has approximately 50-100-fold more procoagulant activity (49). Moreover, MPs are the most important reservoir for blood-borne TF. MPs can transfer and deliver TF to target cells, including platelets and neutrophils, thereby amplifying and disseminating the procoagulant response. As such, notwithstanding their physiological role in the prevention of bleeding, abundant release of procoagulant MPs clearly can contribute to thrombotic events. Mice deficient for lactadherin, an opsonin that is important for the clearance of platelet MPs, have elevated concentrations of circulating MPs and produced two-fold more thrombin (50). Importantly, lactadherin-deficient mice had a shorter venous occlusion time in an endothelial cell injury model, indicating that impaired clearance of platelet MPs results in a hypercoagulable state (50). In accordance, platelet MPs contributed to thrombus growth in a mouse model of venous thrombosis (51).

Bacterial agonists and proinflammatory cytokines can fuel the shedding and the procoagulant properties of MPs. Stimulation of endothelial cells causes shedding of MPs that express ultralarge von Willebrand factor multimers, which potently promote the formation of platelet aggregates and increase their stability (52). Stimulation of monocytes with endotoxin results in the release of TF expressing MPs (53). Accordingly, administration of endotoxin to mice (54) or humans (55) results in the appearance of TF bearing MPs in the circulation, and a variety of studies have reported increased circulating levels of MPs of various cellular origin in patients with sepsis (56-58).

A recent investigation conducted in patients with septic shock found that while total MP levels were high regardless of the presence of DIC, endothelial and leukocyte-derived MPs positively correlated with DIC status (59). The functional relevance of MPs has been demonstrated in a number of in vivo transfer studies. Infusion of MPs harvested from septic rodents reproduced part of the septic host response in healthy animals (60). Similarly, administration of MPs from septic patients induced differential effects in different organs of healthy mice, which at least in part mimicked the organ dysfunction observed in patients with septic shock (61). Conversely, inhibition of MP release through transgenic overexpression of calpastatin, a specific inhibitor of calpain - a protease that plays an essential role in MP release, attenuated the systemic proinflammatory response and DIC in mice with polymicrobial abdominal sepsis by reducing the number of circulating procoagulant MPs (62). It should be noted that MPs are able to develop immunoprotective properties in animal models of sepsis, as they can explore antimicrobial activity, entrap bacteria, and prevent their dissemination from the local focus of infection (63). In addition, increased circulating MPs have been shown to diminish vascular hyporeactivity complications in endotoxin-treated mice (58). It has been therefore suggested that MPs have a beneficial effects during the early phase of sepsis (64).

It is also important to note that MPs have anticoagulant potential. Indeed, anionic phospholipids exposed by MPs can not only assist in the assembly of procoagulant enzyme complexes, but also promote the association of anticoagulant proteins, including TFPI, thrombomodulin, EPCR and protein S. APC can induce MPs from endothelial cells, which support efficient inactivation of factors Va and VIIa facilitated by EPCR expressed by MPs. The release of antocoagulant MPs required both APC and PAR1 active sites and could also be observed on monocyte-derived MPs (65). Several cytoprotective effects linked to APC could be induced by APC positive MPs in vitro (66). Moreover, evidence indicates that the infusion of recombinant human APC, until recently a registered drug for the treatment of severe sepsis, results in an increase in circulating APC positive MPs, suggesting that part of the in vivo effects of APC may be mediated by anticoagulant and cytoprotective MPs (67).

Coagulation and anticoagulation during systemic and local infection

Severe infection can lead to an injurious host response and tissue injury, resulting in the clinical syndrome generally referred to as sepsis (8). The procoagulant response to sepsis is characterized by enhanced coagulation together with impaired anticoagulant mechanisms (68). The main route by which infection and inflammation initiate coagulation is via TF. Indeed, inhibition of the TF/factor VIIa pathway in humans and non-human primates strongly reduced activation of the coagulation system after infusion of endotoxin or bacteria, while in lethal primate sepsis TF inhibition in addition prevented multiple organ failure and mortality (68). In accordance, mice with very low TF expression demonstrated diminished coagulation, inflammation and mortality upon administration of high dose endotoxin (69).

The tendency towards enhanced thrombus formation during severe infection is further increased due to impaired functioning of the three main anticoagulant pathways, *i.e.*, antithrombin, TFPI and the protein C system (68). The regulatory function of the endogenous protein C system in infection has been demonstrated in a variety of studies (70). Inhibition of protein C activation aggravated the response to *Escherichia coli* and converted a sublethal model into a lethal DIC-associated model (71). Similarly, baboons treated with an anti-EPCR monoclonal antibody displayed an exacerbation of a sublethal *Escherichia coli* infection to lethal sepsis with massive coagulation activation (72). Notably, the anticoagulant effects of APC are not essential for prevention of lethality in endotoxemic or septic mice: recombinant APC mutants with selective cytoprotective properties (and almost no anticoagulant effects) were as protective against lethality as wild-type APC (73). Of interest, recombinant APC protected mice against endotoxin-induced lethality by an effect on EPCR and PAR1 in hematopoietic cells (74). By contrast, hematopoietic EPCR deficiency did not increase the susceptibility of mice to endotoxin (74, 75), indicating that the effects of pharmacological doses of (exogenous) recombinant APC on immune cells may be different from the effects of endogenous APC.

Local infection results in hemostatic alterations at the site of the infection that are remarkably similar to those found in the circulation during systemic infection; this has particularly been well-studied in pneumonia (76). Patients with respiratory tract infections demonstrate enhanced activation of coagulation in their bronchoalveolar space together with locally impaired anticoagulant mechanisms (77-79). Mouse studies have revealed the important role of TF in pulmonary coagulation during bacterial pneumonia (79, 80). Interference with local hemostasis has differential

effects on the outcome of experimental pneumonia. In accordance with finding after intravenous infusion of *Escherichia coli* (71), inhibition of endogenous protein C worsened survival, increased coagulation activation, facilitated bacterial growth and dissemination and enhanced the inflammatory response during pneumonia-derived sepsis caused by *Burkholderia pseudomallei*, the causative agent of melioidosis (81). Intriguingly, transgenic overexpression of APC also resulted in enhanced susceptibility to *Burkholderia pseudomallei* infection, as evidenced by a strongly increased mortality accompanied by enhanced bacterial loads and increased inflammation, in spite of attenuated coagulation (82), suggesting that while low endogenous APC levels are essential for an adequate host defense, sustained high APC concentrations are harmful. In support of a potential detrimental effect of APC, mice with transgenic overexpression of EPCR, which is expected to enhance APC generation, showed an impaired host defense during pneumonia caused by either *Streptococcus pneumoniae* (83) or *Burkholderia pseudomallei* (84). Clearly, the exact role of local coagulation and anticoagulation during localized infections requires further research.

Fibrinolysis

Haemostasis is controlled by the fibrinolytic system, which generates plasmin to degrade fibrin clots. Plasmin is generated from the zymogen protein plasminogen by different proteases, in particular tissue-type plasminogen activator (t-PA) and urokinase-type (u-)PA. Other enzymes that can covert plasminogen into plasmin include factor XIIa and kallikrein, thereby linking the contact system with fibrinolysis (85). Besides plasmin, other proteases can degrade fibrin, especially neutrophil elastase, generating cross-linked fibrin fragments that are different from those produced by plasmin. Inhibition of the fibrinolytic system occurs at the level of plasminogen activation by plasminogen activator inhibitors (especially plasminogen activator inhibitor type I or PAI-1), or at the level of plasmin activity by circulating protease inhibitors, of which α2-antiplasmin is the most important. Fibrinolysis is further regulated by thrombin-activatable fibrinolysis inhibitor (TAFI), which is activated by thrombin and the thrombin-thrombomodulin complex on endothelial cells (86). Activated TAFI inhibits fibrinolysis by removing C-terminal lysine and arginine residues from partially degraded fibrin, thereby inhibiting the high-affinity

binding of plasminogen to fibrin and the subsequent facilitated conversion into the active protease plasmin.

Induction of systemic inflammation by either bacteria, bacterial products or proinflammatory cytokines is associated with a transient activation of the fibrinolytic system characterized by a brisk rise in plasminogen activator activity in the circulation, which is subsequently shut off by the systemic appearance of PAI-1 (87). Similar observations have been done in baboons with lethal bacteremia and human sepsis, the net result being suppression of fibrinolysis. While the original assumption was that the fibrinolytic response represents a reaction to the formation of thrombin and fibrin under these conditions, several lines of evidence support the fact that the procoagulant and the fibrinolytic response to systemic inflammation at least in part are induced independently. In humans and nonhuman primates infusion of endotoxin or *Escharichia coli* caused a rapid and transient activation of the fibrinolytic system, as indicated by a marked increase in the plasma concentrations of t-PA, that preceded the activation of the coagulation system (87). In addition, abrogation of coagulation by inhibition of TF or factor VIIa did not affect activation of fibrinolysis during human or primate endotoxemia (87-89). Finally, inhibition of plasmin generation by tranexamic acid did not impact on the procoagulant response to intravenous endotoxin in healthy humans (90). In experimental endotoxemia the fibrinolytic response is dependent on endotoxin-induced tumor necrosis factor (TNF)-α release, as reflected by a strongly inhibited release of both t-PA and PAI-1 in humans and primates injected with endotoxin and treated with a neutralizing anti-TNF-α antibody; this intervention does not influence activation of the coagulation (91, 92). Thus, at least in these systemic challenge models the fibrinolytic response is not directly linked to the clotting cascade.

Impaired fibrinolysis and as a consequence thereof, inadequate fibrin removal are likely to contribute to the development of microvascular thrombosis in sepsis (87). Indeed, the functional relevance of the fibrinolytic system for inflammation-induced coagulation in sepsis has been shown by experiments in genetically modified mice, showing that t-PA and u-PA deficient mice challenged with endotoxin have increased fibrin deposition in their organs compared with wild type mice, while the opposite was true for PAI-1 deficient mice (93). In infection models, components of the fibrinolytic system have been shown to impact on host response pathways distinct from fibrinolysis. While elevated elevated circulating PAI-1 levels are highly

predictive for an unfavorable outcome in sepsis patients (87), investigations using PAI-1 deficient mice and mice with transiently enhanced expression of PAI-1 have pointed to a protective rather than a detrimental role of this mediator in severe Gram-negative pneumonia and sepsis (94). PAI-1 deficiency impaired host defense during *Klebsiella* pneumonia and sepsis as reflected by enhanced lethality and increased bacterial growth and dissemination in mice with a targeted deletion of the *pai-1* gene. Conversely, transgenic overexpression of PAI-1 in the lung using a replication defective adenoviral vector markedly improved host defense against *Klebsiella* pneumonia and sepsis (94). PAI-1 deficiency also impaired host defense in experimental pneumococcal pneumonia (95) and Gram-negative sepsis caused by *Burkholderia pseudomallei* (96). Likewise, deficiency of the other main inhibitor of fibrinolysis α2-antiplasmin resulted in a strongly disturbed host response during *Burkholderia pseudomallei* sepsis, as reflected by enhanced bacterial growth and dissemination, exaggerated systemic inflammation and coagulation, increased distant organ injury, and enhanced lethality (97). Remarkably, t-PA may in some infection models also improve host defense: tPA deficient mice had an impaired defense after infection with either *Escherichia coli* (98) or *Burkholderia pseudomallei* (99), as indicated by higher bacterial loads and a reduced survival. In *Escherichia coli* sepsis, the protective function of t-PA was independent of its capacity to convert plasminogen into plasmin since plasminogen gene deficient mice were indistinguishable from wild-type mice in this model (98). u-PA and its receptor (u-PAR) are involved in cell migration. u-PAR mediates leukocyte adhesion to the vascular wall and components of the extracellular matrix and the expression of u-PAR on leukocytes is strongly associated with their migratory capacity (100). Experiments in u-PAR deficient mice have shown the relevance of this receptor for the regulation of the inflammatory response to infection; for example, u-PAR (but not u-PA) deficient animals demonstrated a strongly diminished neutrophil influx into to lungs after induction of bacterial pneumonia (101).

Some pathogens can activate plasminogen by producing plasminogen receptors and plasminogen activation by complex formation or proteases, and/or by binding plasminogen at their surface with subsequent activation by host-derived t-PA and u-PA (102). Plasmin expressed at the bacterial cell surface can be used by bacteria for proteolyic degradation of extracellular matrix components, thereby facilitating bacterial dissemination to distant organs. Bacteria can also produce plasminogen

activators, *e.g.*, streptokinase produced by group A, C and G streptococci, and Pla produced by *Yersinia pestis* (102). In addition, several glycolytic enzymes expressed by bacteria interact with plasmin(ogen). Discussion of the impact of distinct bacterial enzymes on the virulence of various micro-organisms is beyond the scope of this review (see (102)).

TAFI plays a role in the host response to infection by a mechanism that likely is not linked to its presumptive function as a natural inhibitor of fibrinolysis. TAFI deficient mice did not show differences in *Escherichia coli*-induced activation of coagulation or fibrinolysis in vivo, as measured by plasma levels of thrombin-antithrombin complexes and D-dimer and the extent of fibrin depositions in lung and liver tissues; however, TAFI deficient mice were protected from liver necrosis as indicated by histopathology and clinical chemistry (103).

Conclusions

Recent years have shown that coagulation is much more than a glue that seals an injured blood vessel. While it has been known for a long time that its systemic activation can lead to devastating conditions such as disseminated intravascular coagulation with high mortality rates, an important role of the coagulation system in the early host response to infectious diseases has been only recently begun to be appreciated. The profound knowledge about the molecular mechanisms involved in these processes may help to develop novel therapeutic strategies that not only prevents a systemic induction of the coagulation cascade, but also help to eliminate to the pathogen at a very early time point of the disease progression.

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Conflict of interest disclosure

The authors declare no competing financial interests.

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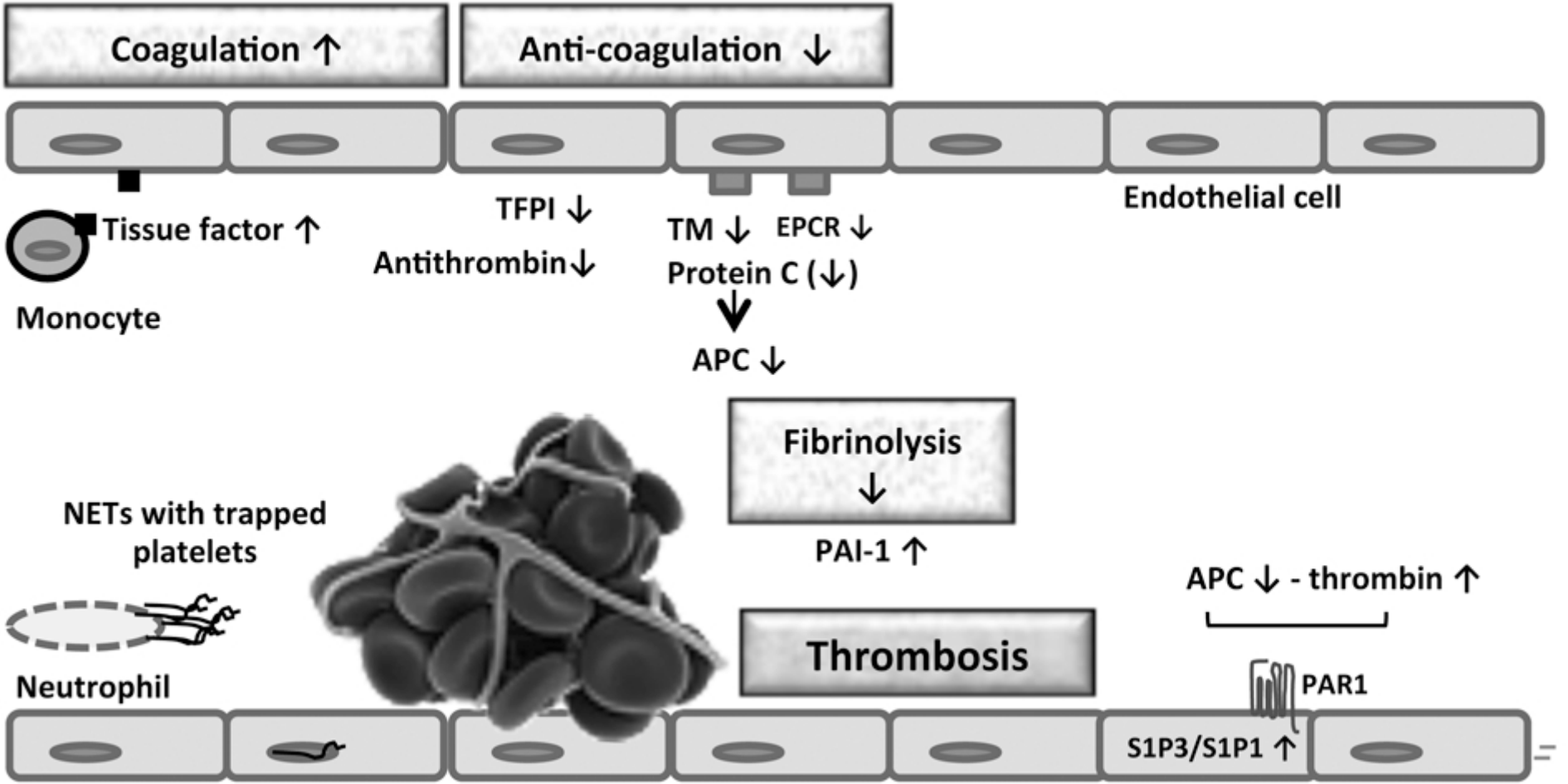
Figure legend

Figure 1: **The disturbed hemostatic balance in sepsis.** Sepsis is associated with microvascular thrombosis due to concurrent activation of coagulation (mediated by tissue factor) and impairment of anticoagulant mechanisms as a consequence of reduced activity of endogenous anticoagulant pathways mediated by activated protein C (APC), antithrombin and tissue factor pathway inhibitor (TFPI), plus impaired fibrinolysis due to enhanced release of plasminogen activator inhibitor type I (PAI-1). The capacity to generate activated protein C is impaired at least in part due to reduced expression of the endothelial receptors thrombomodulin (TM) and the endothelial protein C receptor (EPCR). Thrombus formation is further facilitated by neutrophil extracellular traps (NETs) released from dying neutrophils. Loss of endothelial barrier function is at least in part caused by a disturbed balance between sphingosine 1 phosphate receptor 1 (S1P1) and S1P3 within the vascular wall at least in part due preferential induction of S1P3 via protease activated receptor 1 (PAR1) secondary to a reduced APC/thrombin ratio.

Table1: Procoagulant factors and their role in innate immunity

protein/peptide	function	reference
tissue factor	activation of PAR2 activation of mitogen activated protein kinase family	(1) (2)
tissue factor pathway inhibitor 1/2	antimicrobial activity	(3, 4)
contact system factors	pattern recognition molecules	(5)
high molecular weight kininogen	precursor of peptides with antimicrobial activity	(6, 7)
bradykinin	inflammatory mediator (chronic)	(8)
des-Arg^{9}-bradykinin	inflammatory mediator (acute)	(8)
factor Xa	activation of PAR receptors precursor of peptides with antimicrobial activity	(9) (10)
thrombin	activation of PAR receptors precursor of peptides with antimicrobial activity	(9) (3)
activated protein C	activation of PAR1 receptor	(11)
factor XIIIa	immobilization of bacteria inside a clot	(12)
microparticles (MPs)	antimicrobial activity and entrapment of bacteria diminish vascular hyporeactivity complications	(63) (58)
neutrophil extracelluar traps (NETs)	activation of the contact system adhesion, activation, and aggregation of platelets	(13) (14)
TAFI	conversion of bradykinin to des-Arg^{9}-bradykinin escaping from fibrin-mediated physical entrapment	(110) (111)


Coagulation ↑
Anti-coagulation ↓
Endothelial cell
Tissue factor ↑
Monocyte
TFPI ↓
Antithrombin↓
TM ↓
EPCR ↓
Protein C (↓)
APC ↓
Fibrinolysis
↓
PAI-1 ↑
NETs with trapped platelets
Neutrophil
Thrombosis
APC ↓ - thrombin ↑
PAR1
S1P3/S1P1 ↑