

## REVIEW ARTICLE

# The coagulation system in host defense

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**Abstract**

The blood coagulation system and immune system of higher organisms are thought to have a common ancestral origin. During infections, the blood coagulation system is activated and components of the hemostatic system are directly involved in the immune response and immune system modulations. The current view is that the activation of coagulation is beneficial for infections with bacteria and viruses. It limits pathogen dissemination and supports pathogen killing and tissue repair. On the other hand, overactivation can lead to thrombosis with subsequent depletion of hemostatic factors and secondary bleeding. This review will summarize the current knowledge on blood coagulation and pathogen infection with focus on most recent studies of the role of the different parts of the blood coagulation system in selected bacterial and viral infections.

**KEYWORDS**

coagulation, hemostasis, infection, inflammation, peritonitis, pneumonia

**Essentials**

- Blood coagulation system is activated during infections.
- Components of the coagulation system directly interact with the immune system.
- Activation of coagulation system limits pathogen dissemination and supports pathogen killing.
- Overactivation can contribute to infection pathology due to thrombosis and bleeding complications.

## 1 | INTRODUCTION

### 1.1 | Coagulation cascade

Blood coagulation is initiated by exposure of blood to the transmembrane protein tissue factor (TF).<sup>1</sup> Under normal conditions, TF is not expressed by cells, such as circulating blood cells and endothelial cells, which are in direct contact with plasma-circulating coagulation protease zymogens.<sup>1,2</sup> However, subendothelial cells including pericytes, fibroblasts, and smooth muscle cells constitutively express high levels of TF.<sup>3</sup> This separation of extravascular TF and circulating plasma-clotting factors prevents an inappropriate activation of coagulation under basal conditions. In certain tissues perivascular

TF is already in complex with the plasma coagulation protease FVII/FVIIa which may enhance coagulation initiation.<sup>4</sup> Upon vessel injury, the blood plasma coagulation factors come into contact with the TF:FVIIa complex which converts FX to FXa.<sup>5,6</sup> Importantly, under pathologic conditions TF can also be expressed by monocytes and transferred via membrane-derived microvesicles (MV) to other cells, including endothelial cells, platelets, and possibly neutrophils.<sup>1</sup> The intrinsic pathway consist of FXII, FXI, and FIX with its cofactor FVIII. Historically, it was thought that this pathway is activated by negatively charged artificial and biological surfaces, such as artificial valves and polyphosphates, within the blood independent of vessel injury.<sup>7</sup> The intrinsic pathway is now seen as an amplification loop that enhances generation of FXa through the FIXa:FVIIIa tenase

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complex.<sup>1</sup> FXa forms the prothrombinase complex with FVa and mediates the conversion of prothrombin to thrombin. FXa, its cofactor FVa, and thrombin form the common pathway leading to thrombin-mediated cleavage of fibrinogen to fibrin which is then cross-linked by activated FXIII forming a stable clot.<sup>8</sup>

Nowadays, a clear separation of the extrinsic and the intrinsic pathways is difficult since it was shown that the TF:FVIIa complex can also lead to activation of the intrinsic coagulation protease FIX and thrombin can activate FXI.<sup>9</sup> FXII does not play a role in hemostasis but can contribute to thrombosis as well as inflammatory responses.<sup>10</sup> Importantly, there is an ongoing effort to develop new anticoagulants targeting the intrinsic pathway, since deficiencies or inhibition of FXI- and FXII-reduced thrombosis in experimental and clinical studies without a major impact on hemostasis, e.g., spontaneous bleedings.<sup>10,11</sup>

## 1.2 | Coagulation-dependent signaling

Besides leading to a stable clot, active proteases generated during the coagulation cascade can directly induce cell-specific signaling via the cleavage of protease-activated receptors (PARs).<sup>12</sup> PARs form a receptor family with four members, PAR1-4.<sup>13</sup> Briefly, the TF:FVIIa complex and FXa can activate PAR2.<sup>14</sup> Thrombin is the primary activator of PAR1, PAR3, and PAR4. Further, FXa can activate PAR1. PARs are ubiquitously expressed within the body in similar patterns across mammals.<sup>13,14</sup> However, there is a significant difference between human and rodent PAR expression on platelets. Human platelets express PAR1 and PAR4 whereas murine platelets express PAR3 and PAR4.<sup>14</sup>

Several studies showed that PARs modulate innate immune responses by crosstalk with toll-like receptors (TLRs).<sup>15-19</sup> Antibacterial TLR4 signaling is enhanced by PAR2, whereas PAR2 reduces antiviral responses via TLR3.<sup>15,16,19</sup> This PAR2-dependent TLR modulation is thought to be through direct receptor:receptor interaction.<sup>16,19</sup> In addition, we have shown that coagulation-dependent PAR1 signaling enhances TLR3-dependent antiviral responses.<sup>17,18</sup>

Unfortunately, experimental studies with global PAR-deficient mice were not able to reveal any major contribution of PARs to the pathologies of bacterial infection or endotoxemia.<sup>20</sup> In contrast to bacterial infections, there are clear phenotypes in PAR1- and PAR2-deficient mice in different viral infection models.<sup>14-18</sup> It could be speculated that host proteases, such as thrombin, stimulate the antiviral response via PAR1, whereas viral proteases may activate PAR2 in an attempt to dampen the antiviral response of the host and increase virus infectivity.<sup>17</sup>

Newer mouse models with different cleavage-insensitive PAR1 and PAR2 mutant *knock-in* mice might uncover a biased protease-dependent signaling to certain infections which were hidden in global PAR1 or PAR2 *knock-out* mice.<sup>21,22</sup>

## 1.3 | Infections and the activation of coagulation

The coagulation system is activated in response to infection by a variety of different pathogens, including bacteria and viruses (Tables 1 and 2).<sup>14,18,20,23,24</sup> This response appears to have developed as a host

defense system to limit the spread of the pathogen. During infections, there is an interplay between blood coagulation, immune cells, and platelets to restrict dissemination of pathogens within the body.<sup>9,14,25</sup> Activation of coagulation coincides with the recruitment of leukocytes where clot components, such as fibrin, serve as a scaffold for adherence and migration of cells. Leukocytes themselves can enhance coagulation by expressing TF and by releasing TF+MV. More importantly, neutrophils release neutrophil extracellular traps (NETs) after activation.<sup>9,26</sup> NETs are composed of nuclear DNA, histones, and several neutrophil enzymes including elastase. NETs were shown to have important antibacterial and potential antiviral functions and, due to their negative charge, also a coagulation-enhancing activity.<sup>9,26,27</sup> Thus, leukocytes are thought to be a major player in the cross-communication between blood coagulation and the immune response.

Sepsis is a clinical condition as response to an acute bacterial or viral infection in the blood, with ongoing activation of the immune and coagulation system. Unfortunately, overactivation of the coagulation system in acute bacteremia and viremia can lead to disseminated intravascular coagulation (DIC), microvascular thrombosis-induced hypoxia that contributes to multiorgan failure, septic shock, and death.<sup>24,25</sup> Hemorrhages occur due to consumption of coagulation factors and platelets, resulting from ongoing intravascular activation of the hemostatic system.<sup>28</sup>

Fibrin(ogen) has a central role in hemostasis and thrombosis but it also contributes to multiple physiologic and pathologic processes beyond blood coagulation.<sup>29,30</sup> Reduced fibrin(ogen) levels are a predictor for hemorrhagic complications.<sup>31</sup> In addition, fibrin clots were shown to be a strong inducer of a proinflammatory response of in clot-embedded monocytes and timely degradation via fibrinolysis can dampen this inflammatory response. The reported inflammatory response was thrombin-independent but fibrin-dependent.<sup>32</sup> Innate immune cells responding via the integrin receptor  $\alpha_M\beta_2$  (CD11b/CD18, Mac-1) to the  $\gamma$  chain of fibrin(ogen) by phagocytosis, generation of reactive oxygen species and NF $\kappa$ B-mediated gene expression of proinflammatory mediators.<sup>33</sup> Interestingly, a report showed that soluble fibrin(ogen) can bind and induce signaling in neutrophils independently of Mac-1 in vitro which suggests an additional fibrin(ogen) receptor.<sup>34</sup> Mac-1 was further identified as a surface receptor for dsRNA on macrophages mediating TLR3-dependent and -independent immune responses.<sup>35</sup> The dsRNA:Mac-1 interaction was blocked by treatment of cells with fibrin(ogen).<sup>35</sup> This observation suggests that high levels of soluble fibrin(ogen) might saturate Mac-1 and therefore reduce the innate immune response to dsRNA in viral infection. Finally, fibrin degradation products (FDP) are potent chemotactic signals for neutrophils and other leukocytes.<sup>36,37</sup> In addition, FDP are able to enhance as well as inhibit platelet function/aggregation.<sup>38</sup>

In the past, research was focused on the effect of endotoxemia and bacteremia/sepsis on the coagulation system with regards to DIC, septic shock, and bleeding complications. Newer studies have tried to understand its protective role in viral infections, such as H1N1 influenza A virus (IAV), Ebola virus, and emerging viral pathogens including Dengue and Zika virus.<sup>14,23,25,39-42</sup>

**TABLE 1** Role of the blood coagulation system in bacterial infections

Infection	Observation	References
Bacterial pneumonia	<ul style="list-style-type: none"> <li>• Bacterial infection of lung and endotoxemia leads to local activation of coagulation</li> <li>• Lung epithelial TF maintains tissue hemostasis after local LPS challenge</li> <li>• Local FVIIa administration reduces pulmonary bleeding</li> <li>• Myeloid TF does not contribute to activation coagulation in lungs after local LPS challenge</li> <li>• Myeloid TF has no role in lung injury after <i>Klebsiella</i> infection</li> <li>• Myeloid TF reduces macrophage recruitment into lung after local LPS challenge</li> <li>• Myeloid TF reduces lung CXCL1 expression during <i>Klebsiella</i> infection</li> <li>• Myeloid TF controls <i>Mycobacterium tuberculosis</i> growth but global TF deficiency (LowTF mice) has no effect</li> <li>• FXII<sup>-/-</sup> mice are protected in <i>Klebsiella</i> pneumonia</li> <li>• FXII/FXIIa has no effect on murine and human neutrophil phagocytosis</li> <li>• FXII does not contribute to coagulation activation in <i>Klebsiella</i> and <i>Streptococcus pneumoniae</i></li> <li>• FXI deficiency results in higher mortality during <i>Klebsiella</i> and <i>Streptococcus pneumoniae</i> associated with higher bacterial out growth and inflammatory response</li> <li>• FXI does not contribute to coagulation activation in <i>Klebsiella</i> and <i>Streptococcus pneumoniae</i></li> <li>• FXIa is needed for phagocytosis of bacteria by murine and human neutrophils</li> <li>• FXI might be activated by thrombin generated via the extrinsic pathway</li> <li>• Thrombin inhibition by dabigatran etexilate increased <i>Klebsiella</i> infection but has no effect on activation of coagulation, thrombocytopenia and fibrin deposition</li> <li>• Thrombin mediated platelet:neutrophil interaction is needed to limit <i>Klebsiella</i> growth</li> <li>• Fibrin degradation/clot lysis due to bacterial proteases leads to increased bleeding tendencies in cystic fibrotic lungs</li> </ul>	20,48,54-58,60,64
Bacterial peritonitis	<ul style="list-style-type: none"> <li>• Myeloid and perivascular TF contributes to systemic activation of coagulation</li> <li>• TF contributes to tissue injury and mortality during sepsis</li> <li>• TF inhibition mediates survival benefits in endotoxemia</li> <li>• FVII consumption causes bleeding and decrease survival</li> <li>• FXIIa inhibition does not reduce DIC induced by <i>E. coli</i> infection</li> <li>• FXIIa inhibition reduces septic-induced hypotension and shock</li> <li>• CLP leads to FXI-dependent FXII activation</li> <li>• FXI<sup>-/-</sup> mice have increased survival associated with reduced inflammation in CLP</li> <li>• FXI does not contribute to CLP-mediated DIC</li> <li>• Thrombin inhibition does not reduce end-organ damage in sepsis</li> <li>• FV Leiden<sup>+/-</sup> mice have survival advantage in endotoxemia and sepsis caused by <i>Staphylococcus aureus</i> and <i>Yersinia pestis</i> but not CLP and <i>E. coli</i> infection</li> <li>• Fibrin deposition limit bacterial dissemination</li> <li>• Fib<sup>AEK</sup> mice exhibit reduced <i>S. aureus</i> clearance</li> <li>• Fib<sup>γ</sup><sup>Δ5</sup> mice exhibit improved survival after <i>S. aureus</i> infection</li> </ul>	20,26,29,44,58,68-73,75,76,78
Bacterial Skin Infection	<ul style="list-style-type: none"> <li>• FV and fibrinogen deficiency results in increases <i>Streptococcus pyogenes</i> infection</li> <li>• FXIII<sup>-/-</sup> mice exhibit increased <i>Streptococcus pyogenes</i> infection</li> <li>• FXIII needed to immobilize bacteria by crosslinking bacterial proteins to fibrinogen/fibrin</li> <li>• FXIII mediates innate immune responses to <i>S. pyogenes</i> infection</li> </ul>	79-81

Studies showed that vascular TF expression can be induced by pathogen-associated molecular patterns, including bacterial lipopolysaccharides (LPS) and viral dsRNA which leads to activation of coagulation in vitro and in vivo.<sup>43,44</sup> TF expressed by monocytes/macrophages is the major source of pathologic TF in bacteremia/sepsis and endotoxemia that leads to aberrant coagulation and inflammation.<sup>20,44</sup> The contribution of endothelial cells to activation of coagulation through expression of TF in vivo is controversial.<sup>1,2</sup> In addition, TF is associated with NETs suggesting a direct link between NETs and the extrinsic pathway.<sup>1,45</sup> Neutrophil elastase, which is released during sepsis, can degrade tissue factor pathway inhibitor, the inhibitor of the TF pathway, which may further enhance coagulation.<sup>26</sup> Furthermore, case studies reported that FVII consumption and uncontrolled bleeding during sepsis can be reduced and

survival improved by systemic administration of additional FVIIa.<sup>46,47</sup> Occurrence of diffuse pulmonary bleeding can be reduced by local administration of FVIIa into the airspace of the lung.<sup>48</sup>

The role of the intrinsic pathway of coagulation in inflammatory responses was recently summarized in detail by others.<sup>10,49</sup> However, there are only limited data available on the role of the intrinsic coagulation pathway and its members FIX, FXI, and FXII in immune responses to viral infections. Studies proposed that depending on the mode of activation, FXII can either trigger blood coagulation via activation of FXI or activate the kallikrein-kinin system (KKS). When FXII is bound to an activating surface, the classic activation, FXII is cleaved and activated by plasma prekallikrein/kallikrein in complexing with high molecular weight kininogen (HK) which subsequently leads to FXIa generation.<sup>10,50</sup> In addition, enveloped viruses were

**TABLE 2** Role of the blood coagulation in viral infections

Infection	Observation	References
Viral pneumonia	<ul style="list-style-type: none"> <li>Increased TF expression in the lung</li> <li>Local and systemic activation of coagulation</li> <li>Reduced levels of TF cause increased pulmonary bleeding and mortality in H1N1 IAV infected mice</li> <li>Lung epithelial TF maintains lung hemostasis in H1N1 IAV infected mice</li> <li>Myeloid as well as endothelial/hematopoietic cell TF does not contribute to activation of coagulation in lungs during sub-lethal H1N1 IAV infection in mice</li> <li>TF+ MV are associated with increased mortality in severe H1N1 IAV infected patients</li> <li>FXII<sup>-/-</sup> exhibited increased mortality during H1N1 IAV infection</li> <li>FIX deficiency has no effect survival during H1N1 IAV infection</li> <li>Thrombin inhibition with dabigatran etexilate has no effect on survival but reduced local activation of coagulation after H1N1 IAV infection in mice</li> <li>Warfarin increases pulmonary hemorrhages and death in H1N1 IAV infected mice</li> <li>Warfarin increases vascular permeability in H1N1 IAV infected mice lungs</li> <li>Reduced fibrinogen/fibrin levels lead to increased H1N1 IAV infection in mice</li> </ul>	23,39,82,83
HIV	<ul style="list-style-type: none"> <li>HIV infection is associated with activation of coagulation</li> <li>HIV leads to TF expression on CD14<sup>+</sup> CD16<sup>-</sup> CCR2<sup>+</sup> monocytes</li> <li>Higher cardiovascular risk in controlled HIV infection when D-dimer is increased</li> <li>On-going thrombin-PAR1 signaling on CXCR1<sup>+</sup> CD8<sup>+</sup> T cells in HIV</li> <li>Thrombin-PAR1 signaling enhance anti-viral responses to dsRNA in mice</li> <li>Thrombin increases T cell receptor mediated IFN<math>\gamma</math> expression on CD8<sup>+</sup> T cells</li> <li>Thrombin-PAR1 signaling increases T Cell motility and cytokine expression</li> </ul>	17,87-93

shown to enhance intrinsic pathway activation in vitro.<sup>51</sup> However, FXII can also be activated by an alternative mechanism via proteases, including elastase and plasmin.<sup>50</sup> Certain bacteria were shown to express specific LPS, polyphosphates, elastase, or plasminogen activators to trigger bradykinin production via FXII activation.<sup>50,52,53</sup> The alternative activation mechanism of FXII results in a significant reduced activation of coagulation and shifting FXIIa towards its pro-inflammatory role.<sup>50</sup>

The remainder of this review will focus on the role of the coagulation cascade in infections with selected pathogens with particular attention paid to the intersection of the hemostatic system with antibacterial and antiviral immune responses (Tables 1 and 2).

## 1.4 | Bacterial pneumonia

Pneumonia studies with the Gram-negative *Klebsiella pneumoniae* or the Gram-positive *Streptococcus pneumoniae* are widely used to investigate local pathogen-host interactions (Table 1). Both bacteria were shown to lead to local activation of coagulation and fibrin deposition in the lungs.<sup>54,55</sup> Interestingly, while systemic inhibition of TF was beneficial in sepsis and endotoxemia, a global deficiency of TF (LowTF mice) during LPS administration into the lung led to increased pulmonary hemorrhages and lung inflammation.<sup>20,56</sup> Tissue hemostasis and lung-dependent activation of coagulation during local endotoxemia is mediated by TF expressed on lung epithelial cells and not myeloid cells.<sup>57</sup> However, TF deficiency on both cell types did not significantly affect local lung inflammation.<sup>57</sup> In line with this, myeloid TF had no effect on *Klebsiella pneumoniae*-induced lung injury.<sup>58</sup> Notably, a lack of myeloid TF increased the expression of KC/CXCL1, a neutrophil chemoattractant and the murine homolog to human IL-8, in the lung after *Klebsiella* infection and local LPS

administration.<sup>57,58</sup> This suggests that myeloid TF is a negative regulator for macrophage infiltration into the alveolus during bacterial infection.<sup>57</sup> Moreover, Kral-Pointner et al reported in acid-induced lung injury a myeloid TF-dependent anti-inflammatory effect within the lung. Mice lacking myeloid cell TF exhibited increased neutrophil accumulation in the lung. Furthermore, in vitro studies showed that myeloid TF dampened NF $\kappa$ B-dependent responses after hydrochloric acid stimulation.<sup>59</sup> Interestingly, in infection, myeloid TF was needed to control bacterial growth.<sup>60</sup> A lack of myeloid cell TF resulted in less fibrin deposition and a M2 macrophage phenotype within the lung.<sup>60</sup> However, when using a global TF deficient mouse (LowTF mice) this difference was not detectable which could be due a low but still sufficient TF expression in macrophages.<sup>61</sup> Further, Rauch's group found that the FXa inhibitor fondaparinux increased a M2 macrophage phenotype in the mouse heart during viral myocarditis.<sup>62</sup> This suggest that myeloid expressed TF suppresses the differentiation into an anti-inflammatory M2 macrophage. It is not clear if this TF:FXa effect is PAR-dependent.

Stroo et al used FXI and FXII deficient mice to investigate the role of both factors in *Klebsiella* and *Streptococcus pneumoniae* and found that a lack of FXI resulted in higher mortality and enhanced bacterial outgrowth in both models.<sup>55</sup> This observation was accompanied by increased inflammatory responses in FXI<sup>-/-</sup> mice.<sup>55</sup> In contrast to the findings with FXI<sup>-/-</sup> mice, FXII<sup>-/-</sup> mice were protected only in *Klebsiella pneumoniae* associated with improved survival and reduced bacterial burden. Both models showed that a deficiency of either FXI or FXII did not reduced the local activation of coagulation. Furthermore, the authors reported that active FXI was needed for phagocytosis of bacteria by murine and human neutrophils, whereas FXII or FXIIa-dependent FXI activation had no effect on phagocytosis.<sup>55</sup>

It was shown that thrombin activity leads to endothelial cell activation in *Klebsiella* infection.<sup>54</sup> Interestingly, thrombin inhibition and fibrin depletion resulted in increased *Klebsiella* infection in mice associated with increased bacterial outgrowth and dissemination leading to higher mortality.<sup>54</sup> However, the thrombin inhibitor dabigatran had no effect on neutrophil recruitment, activation, and NET formation, but it dampened coagulation activation measured by reduced D-dimer and thrombin-antithrombin (TAT) levels, and fibrin depositions within the lung.<sup>54</sup> Whole blood assays showed that the combination of active thrombin, platelets, and neutrophils were essential to limit *Klebsiella* growth.<sup>54</sup> Interestingly, the authors observed that thrombin-mediated PAR1 activation on platelets reduced *Klebsiella* growth in human blood by enhancing platelet-neutrophil interaction.<sup>54</sup> Further, thrombin inhibition reduced platelet-neutrophil interaction in *Klebsiella* pneumonia but did not effected thrombocytopenia.<sup>54</sup>

These findings suggested that extrinsic pathway generated thrombin mediates fibrin polymerization and platelet-neutrophil interactions are essential for protective immune responses in at least *Klebsiella* pneumonia-derived sepsis.<sup>54</sup> Furthermore, FXI is activated by extrinsic pathway generated thrombin independently of FXIIa in bacterial pneumonia which influences the antibacterial function of neutrophils.<sup>55</sup>

Importantly, bacteria can support the activation of plasminogen on their surface.<sup>63</sup> Increased clot lysis and fibrin degradation would lead to bacterial dissemination. Cystic fibrosis is associated with specific bacterial colonization of the lung and can cause hemoptysis a hallmark of "cepacia syndrome".<sup>64</sup> Within the cystic fibrosis lung, bacterial proteases as well as neutrophil elastase are generated/released which were shown to degrade fibrin.<sup>64</sup> Cystic fibrosis hemoptysis is therefore a result of infection-driven immune responses causing a failure of lung integrity and affecting lung hemostasis, which subsequently leads to hemorrhages into the airway lumen during the phase of acute infection.<sup>64-66</sup>

## 1.5 | Bacterial peritonitis

To analyze the effect of systemic bacteremia/sepsis and endoxemia, mice are subjected to intraperitoneal or intravenous injection of bacteria or endotoxin as well as cecal ligation and puncture (CLP) surgery. The majority of the studies that have analyzed the role of the coagulation system in peritonitis and sepsis use *Staphylococcus aureus*, *Yersinia pestis* and *Escherichia coli* (Table 1). The interaction between the host's coagulation/immune system and *S. aureus* were extensively reviewed recently in detail.<sup>67</sup> It was repeatedly shown that the TF pathway is essential for the induction of coagulation in endotoxemia and sepsis, which subsequently leads to tissue injury and mortality.<sup>20,44,68,69</sup> Further, inhibition of TF-dependent activation was reported to improve survival in endotoxemia and sepsis.<sup>20</sup> The major contributor in endotoxemia induced systemic coagulation activation is TF expressed by myeloid cells as well as by cells of unknown perivascular origin.<sup>44</sup> Interestingly, Bastarache's group was not able to show that myeloid TF had any role in indirect lung injury

during endotoxemia and CLP sepsis.<sup>58</sup> In addition, the prothrombotic phenotype of FV Leiden heterozygosity in mice poses a survival advantage in endotoxemia and sepsis caused by *S. aureus* and *Y. pestis* but not by CLP or *E. coli*.<sup>70,71</sup> The authors proposed that FV Leiden has anti-fibrinolytic effects which opposes the bacterial fibrinolytic virulence factors.<sup>70</sup> Interestingly, endothelial PC receptor deficiency but not PAR1 deficiency abrogated the survival advantage of heterozygous FV Leiden mice.<sup>70</sup>

It seems that the intrinsic pathway does not play any significant role in the activation of coagulation but contributes to inflammation during sepsis. For instance, an anti-FXIIa antibody or FXI deficiency did not block *E. coli* or CLP-induced DIC, respectively.<sup>72,73</sup> Only one study showed that inhibition of FXIIa-dependent FXI activation via the inhibitory antibody 14E11 reduced thrombin generation, platelet consumption, cytokine expression and resulted in improved survival of CLP mice.<sup>74</sup> Furthermore, FXIIa inhibition reduced sepsis-induced hypotension and shock.<sup>50</sup> Also, FXIa was shown to induce cytokine responses after CLP in mice.<sup>73,74</sup> Thus, FXI<sup>-/-</sup> mice exhibited increased survival with reduced CLP-induced cytokine expression compared to WT mice. Furthermore, FXIa can activate FXII leading to enhanced activation of the intrinsic pathway and KKS.<sup>73</sup> Indeed, CLP caused a reduction in FXII and prekallikrein plasma levels in WT mice but not FXI<sup>-/-</sup> mice.<sup>73</sup> These data suggest that FXI or FXII inhibition might be beneficial by reducing inflammatory responses in polymicrobial abdominal sepsis but not in bacterial infection of the lung.<sup>55,73,74</sup>

Studies showed an important role for fibrin(ogen) and FXIII to limit bacterial dissemination (Table 1).<sup>26,29,75,76</sup> To analyze the role of fibrin in bacterial infections, Prasad and colleagues generated mice carrying a thrombin-cleavage resistant fibrinogen A $\alpha$  chain (Fib<sup>AEK</sup>). While these mice have normal levels of circulating fibrinogen levels and support normal platelet:fibrinogen interaction they are unable to produce fibrin polymers.<sup>77</sup> Interestingly, Fib<sup>AEK</sup> mice exhibited a profound impediment in *S. aureus* clearance following intraperitoneal infection similar to Fib<sup>-/-</sup> mice but had a significant infection dose-dependent survival advantage over Fib<sup>-/-</sup> mice following peritonitis challenge.<sup>77</sup> This indicates that the fibrin polymerization is critical for the antibacterial action while circulating fibrinogen has additional protective functions possible due to platelet interaction. In addition, mice lacking the last five amino acids of the fibrinogen  $\gamma$  chain (Fib $\gamma$ <sup>A5</sup>) exhibited improved survival after *S. aureus* infection compared to WT and Fib $\gamma$ <sup>390-396A</sup>.<sup>78</sup> Platelet and platelet integrin receptor subunit  $\alpha_{IIb}$  deficient mice established that the survival benefits observed in Fib $\gamma$ <sup>A5</sup> mice were largely independent of platelet  $\alpha_{IIb}\beta_3$ -mediated engagement of fibrinogen.

## 1.6 | Bacterial skin infection

Skin infection with *Streptococcus pyogenes* (Group A streptococcus) is a major public health concern. While local infection is mostly uncomplicated, a systemic dissemination is associated with streptococcal toxic shock syndrome. Ginsburg's group reported that FV and fibrinogen deficiency in mice resulted in increased *S. pyogenes*

infection, suggesting that FV-dependent fibrin deposition was needed to reduce pathogen dissemination (Table 1).<sup>79</sup> However, FV Leiden had no effect on *S. pyogenes* infection.<sup>79</sup>

In line to the findings with fibrinogen deficiency, FXIII deficiency during *S. pyogenes* infection evokes a pathologic inflammatory reaction causing massive neutrophil influx at the site of infection.<sup>80</sup> In addition, FXIII is essential for immobilization of bacteria, such as *S. pyogenes*, within the fibrin network which prevents bacterial dissemination and reduced inflammatory overreaction.<sup>81</sup> Furthermore, local FXIII application at the site of infection resulted in a reduction bacterial dissemination indicating that FXIII mediates protection during early *S. pyogenes* skin infection by supporting early innate immune response.<sup>81</sup>

There are compelling data that reducing coagulation activation can improve the outcome in endotoxemia (Table 1). On the other hand, during bacterial sepsis the activation of coagulation and local thrombosis/fibrin deposition can improve host survival by limiting dissemination of certain bacteria species, including *K. pneumoniae*, *S. pneumoniae*, *S. pyogenes* and *E. coli*. In general, fibrin generation initiated by the host leads to bacterial entrapment reducing bacterial dissemination and increasing pathogen killing by leukocytes. Only a few bacterial pathogens, such as *S. aureus*, developed virulence factors to initiate fibrin generation for evade immune system recognition.<sup>67</sup>

## 1.7 | Viral pneumonia

Recently, we showed that TF is induced in the lung after H1N1 IAV infection in mice which led to increased activation of coagulation via increased TF activity in the lung and by TF+MV in the bronchoalveolar lavage fluid (BALF) (Table 2).<sup>23</sup> The induction of TF and activation of coagulation was abolished in mice with a global TF deficiency (LowTF mice) and mice with a TF deletion in lung epithelial cells suggesting that lung epithelial cells are the main source for inducible TF in the lung and driver of coagulation after H1N1 IAV infection.<sup>23</sup> Furthermore, LowTF mice and mice lacking lung epithelial cell TF presented with increased alveolar hemorrhages and death in sub-lethal H1N1 IAV infection.<sup>23</sup> Importantly, we could not find any contribution for myeloid, endothelial, or hematopoietic TF on the activation of coagulation nor survival after H1N1 IAV infection.<sup>23</sup> The current studies indicating that H1N1 IAV infection is a hemostatic challenge and epithelial cell TF-dependent fibrin deposition mediates lung hemostasis.<sup>23,39</sup> Indeed, reduction of fibrin(ogen) levels with the snake venom ancrod led to an increase of H1N1 IAV infection pathology in mice.<sup>82</sup> However, during severe H1N1 IAV infection, increased TF levels, possible on macrophages, can be deleterious due to increased TF activity on MV in plasma which was associated with increased mortality in H1N1 IAV infected patients.<sup>83</sup>

We found that dabigatran decreased activation of coagulation in the lung measured by TAT levels in the BALF of H1N1 IAV infected mice which was associated with increased pulmonary hemorrhages.<sup>39</sup> However, we could not find any differences in the survival between dabigatran and placebo treated H1N1 IAV infected mice.<sup>39</sup> Importantly, we observed that anticoagulation with the vitamin-K

antagonist warfarin increased pulmonary hemorrhages and mortality of H1N1 IAV infected mice.<sup>39</sup> Anticoagulation with warfarin unselective reduces the vitamin K-dependent procoagulant factors prothrombin, FVII, FIX, FX, and the anticoagulant factors protein C and S, whereas dabigatran only inhibits thrombin activity. APC and FVII were shown to facilitate vascular protection via the endothelial protein C receptor and PAR1 in certain disease models. We found that warfarin but not dabigatran significantly increased vascular permeability in the lung after H1N1 IAV infection compared to H1N1 IAV alone.<sup>39</sup> In support of our findings, APC administration reduced Dengue virus mediated endothelial permeability and inflammatory response,<sup>84</sup> which suggests that APC may be protective during Dengue virus and possible other viral infections. However, the action of APC might be more complicated since inhibition of APC was shown to worsen lung histopathology but lowered neutrophil influx and delayed mortality during lethal IAV infection in mice.<sup>85</sup> We found that PAR1<sup>-/-</sup> mice exhibited increased inflammation in the lung early after H1N1 IAV infection.<sup>18</sup> However, thrombin inhibition had no effect on inflammation and survival after H1N1 IAV infection suggesting that thrombin might not be the major PAR1 activator in this model.<sup>39</sup> As mentioned before, cleavage-resistant PAR1 knock-in mice might reveal the relative contribution of thrombin- vs APC-dependent PAR1 activation in H1N1 IAV infections.<sup>21</sup>

With regard to the intrinsic pathway in H1N1 IAV infection, we reported that FIX deficiency had no effect on survival after infection.<sup>23</sup> Interestingly, we observed that lack of FXII in mice increased the mortality after sub-lethal H1N1 IAV infection (Tatsumi et al, unpublished data). This discrepancy suggests that the intrinsic part of the blood coagulation was not needed to contribute to hemostasis-dependent survival after H1N1 IAV infection.<sup>23</sup> However, it is possible that FXIIa-dependent activation of the KKS mediates protection in H1N1 IAV infection. Surprisingly, we were not able to see any differences in the survival between HK deficient and WT control mice suggesting that FXII-dependent KKS activation is not needed for a positive outcome after H1N1 IAV infection (Tatsumi et al, unpublished data). There might be important FXII function independent of FXI and the KKS which could explain the higher mortality in FXII<sup>-/-</sup> mice in H1N1 IAV infection. For instance, neutrophils were shown to express FXII and that the FXII zymogen acts via uPAR as modulator of neutrophil adhesion and chemotaxis.<sup>86</sup> Unfortunately, the lack of in vivo studies makes it difficult to definitely conclude if the intrinsic pathway has any significant role in viral infections.

## 1.8 | HIV

HIV infection is associated increased TAT and D-dimer levels in plasma suggesting an ongoing activation of coagulation in HIV infection (Table 2).<sup>87-89</sup> Further, the coagulation activation marker correlated with virus load and monocyte TF expression in HIV-infected patients.<sup>90</sup> Interestingly, TF expression seems to be restricted to CD14<sup>+</sup> CD16<sup>-</sup> CCR2<sup>+</sup> monocytes.<sup>91</sup> Thrombin mediates the cross-talk between the coagulation system and the adaptive immune system at sites of vascular injury via PAR1 increasing T cell motility and



proinflammatory cytokine production.<sup>92</sup> Importantly, HIV-infected antiretroviral therapy recipients exhibit, even with suppressed viremia, increased risk for cardiovascular disease due to ongoing thrombin-mediated signaling through PAR1 on CXCR1<sup>+</sup> CD8<sup>+</sup> T cells.<sup>93</sup> Thrombin further directly enhanced T cell receptor-mediated interferon (IFN)  $\gamma$  production by purified CD8<sup>+</sup> T cells.<sup>93</sup>

Currently, there are two ongoing clinical studies with FXa inhibitor edoxaban (TACTICAL-HIV, NCT02339415) or the PAR1 inhibitor vorapaxar (ADVICE, NCT02394730) in patients with HIV infection who are successfully treated with combination antiretroviral therapy. Both studies will compare the safety and efficacy of either edoxaban or vorapaxar in reducing markers of immune system activation in HIV disease. In support of these studies, we showed that thrombin inhibition with dabigatran or PAR1 deficiency reduced the innate immune responses in virus-like stimulation with a dsRNA mimetic in mice.<sup>17</sup>

## 2 | CONCLUSION

In the past, studies have tried to understand whether the activation of coagulation during infections was merely a side effect contributing to infection pathology or if it is an active part in the host's immune response to the pathogen. Nowadays, it is accepted that there is a continuous crosstalk between the immune system with blood coagulation components. Both systems are closely intertwined and essential for an effective immune response to limit the infection. However, as with all fine-tuned systems, once out of control, overactivation can outweigh the beneficial effects by inducing thrombotic complication, excessive inflammation, and tissue damage. Further studies should investigate how to avoid the coagulation overactivation without compromising the beneficial contribution. With regard to the potential clinical significance, it is possible that interference with the PAR1 pathway by direct thrombin inhibitors or PAR1 inhibitors may increase the risk and severity of viral infection, whereas FXa or PAR2 pathway inhibition could mediate a beneficial outcome.<sup>14,62</sup> However, the importance of the PAR1 and PAR2 signaling pathway might be only applicable for an initial viral infection or in immunocompromised individuals. Importantly, there are conflicting data about if the FXa inhibitor rivaroxaban increases the occurrence of early periprosthetic joint infections.<sup>94,95</sup> A recent meta-analysis for the risk of infection with new oral anticoagulants did not find any association.<sup>96</sup> However, the authors stressed that their analysis was limited due to the potential selective reporting bias in the analyzed studies.<sup>96</sup> Further large prospective studies should properly address if the new oral anticoagulants increase the risk for certain bacterial or viral infections.

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The author has nothing to disclose.

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