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Oehmcke, Sonja; Herwald, Heiko

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Contact System Activation in Severe Infectious Diseases

Sonja Oehmcke[#] and Heiko Herwald

From the Department of Clinical Sciences, Division of Infection Medicine, Lund University, SE-22184 Lund, Sweden.

[#]To whom correspondence should be addressed: Department of Clinical Sciences, Division of Infection Medicine, BMC, B14, Lund University, Tornavägen 10, SE-221 84 Lund, Sweden, Phone +46-46-2228592, Fax +46-46-157756, e-mail sonja.oehmcke@med.lu.se

Abstract

Hemostasis is a sensitive and tightly regulated process, involving vascular endothelium and blood cells as well as factors of the coagulation and fibrinolytic cascades. In severe and invasive infectious diseases the equilibrium between the procoagulant and anticoagulant status of the host may change dramatically and can induce life-threatening complications. A growing body of evidence suggests that the contact system, also known as the intrinsic pathway of coagulation or kallikrein/kinin system, participate in these processes. Contact activation leads to the release of the highly potent proinflammatory peptide bradykinin and initiates the intrinsic pathway of coagulation. Several studies have shown a systemic activation of the contact system in animal models of severe bacterial infections and similar findings were also reported when monitoring patients suffering from sepsis, severe sepsis, or septic shock. Complications resulting from a systemic activation of the contact system are pathologically high levels of bradykinin, consumption of contact factors, and a subsequent induction of inflammatory reactions. These conditions may contribute to serious complications such as hypotension and vascular leakage. Here we summarize the state of the art in this field of research with a focus on the contact system and we also discuss a potential role for the contact system as a target for the development of novel antimicrobial strategies.

Introduction

Sepsis, severe sepsis, and septic shock are complications derived from bacterial infections that are the second leading cause of death among patients in non-coronary intensive care units and the 10th leading cause of death in the United States [1]. Despite treatment with antibiotics and an improved intensive care system, the incidence of sepsis and the number of sepsis-related deaths are increasing and they are associated with mortality rates between 30 and 70% [2]. The molecular mechanisms behind the pathogenesis of these life-threatening conditions are still not fully understood. A growing body of evidence, however, suggests that the interaction between bacterial pathogens and the host defense machinery results in an uncontrolled and overwhelming inflammatory response. This includes a systemic activation of proteolytic host cascades such as the complement and coagulation cascades as well as the contact system, also known as the kallikrein/kinin system or intrinsic pathway of coagulation [3].

The contact system

Once activated the contact system is involved in the regulation of hemostatic and inflammatory processes [4, 5]. The system contains 4 components: three serine proteinases: factor XI (FXI), factor XII (FXII), plasma kallikrein, and the non-enzymatic co-factor, high molecular weight kininogen (HK), respectively. The latter protein consists of six domains, of which domain 1 – 3 are cystatin-like. The bradykinin sequence is found in domain 4, and domain 5 carries a zinc-binding site and a binding site for negatively charged surfaces [4-7]. As early as 1995 it was shown that HKH20, a peptide derived from HK domain 5 (amino acids 479 to 498), spanning the binding site for negatively charged surfaces, is able to interact with M protein, an important streptococcal virulence factor [6]. Thereafter, it was also reported that HKH20 mimics the HK binding site to many eukaryotic cell types [8-10], binds to lipopolysaccharide [11], and has antimicrobial activity [12]. In addition another HK-derived peptide (amino acids 420 to 513) covering the HKH20 sequence was found to down-regulate endothelial cell proliferation and migration and inhibit angiogenesis [13]. Finally, domain 6 mediates the binding to plasma kallikrein and FXI [14].

The four contact factors normally circulate in the bloodstream or are bound to the surface of different cell types, including endothelial cells, platelets and polymorphonuclear neutrophils (PMNs). Negatively charged surfaces such as kaolin and dextran-sulfate as well as nucleotides (DNA and RNA) have been reported to assemble and activate the contact system [10, 15-17]. While the molecular

mechanisms leading to a contact activation on kaolin and dextran-sulfate are more or less understood, there are controversial reports addressing the mode of activation on cellular surfaces. Therefore, the latter will not be discussed in this article. FXII bound to kaolin is converted into an active proteinase (FXIIa) by autoactivation. This is followed by a FXIIa-mediated activation of plasma kallikrein, a process referred to as limited proteolysis. Plasma kallikrein in turn is able to increase of the activity of FXIIa, which then enables FXIIa to activate FXI and subsequently the intrinsic pathway of coagulation (Fig.1) eventually leading to the formation of a fibrin network.

Inflammatory reactions are evoked by the processing of HK via plasma kallikrein, resulting in the release of bradykinin (BK) from its precursor. BK is a potent multifunctional pro-inflammatory peptide consisting of nine amino acids. Many effects of BK are induced by its ability to trigger the induction of second-generation mediators such as nitric oxide, prostaglandins and leukotrienes. In addition BK is involved in many other processes such as the regulation of blood pressure, induction of fever, increase of vascular permeability and capillary leakage, edema formation, and hypotension [4, 5]. Notably, the half-life of BK in the circulation is extremely short (< 10 seconds) and thus, increased levels of BK in patients with various underlying diseases are difficult to monitor. There are, however, two conditions that are associated with high levels of BK namely hereditary angioedema (caused by a deficiency of C1-inhibitor, an inhibitor of the contact and the complement system) and severe infectious diseases (for reviews see [18, 19]).

Sepsis and Coagulation

Sepsis is defined as a systemic inflammatory response syndrome (SIRS) with an underlying infection. Complications from these life-threatening conditions are often expanded when the initial appropriate host response to the invading pathogen is amplified and becomes deleterious. Clinical symptoms of the onset are frequently conflictive (fever or hypothermia, tachycardia, leukocytosis or leucopenia), and if untreated, patients may develop respiratory or renal failure, coagulopathy and non-responsive hypotension. The immunological reactions under these conditions are complex and can alter over time. The early proinflammatory response is characterized by an overwhelming stimulus and triggers PMNs and macrophages to an excessive production of cytokines, chemokines, and other proinflammatory mediators. Other complications, such as secondary ischemia (shock) and hypoxia (lung injury) can also amplify the proinflammatory response [20]. This boost of inflammatory reactions may lead to a shift from a normally beneficial inflammatory response to hyper-inflammatory and counterproductive reactions, which eventually

1 cause more damage than the host can tolerate. It is now believed that the initial
2 hyper-inflammatory phase accounts for some early deaths, although most patients
3 die at later stages due to their prolonged immunosuppressive state [21].

4 Studies of host-parasite interactions taking place in the circulation have significantly
5 contributed to our understanding of the molecular mechanisms that lead to the
6 induction of systemic inflammatory reaction. Host effectors systems that are of
7 interest here are the contact-, complement-, fibrinolytic-, and coagulation systems.
8 The latter is activated by the induction of tissue factor (TF) expression on
9 mononuclear and endothelial cells, which is often triggered by bacteria or bacterial
10 products [22]. An up-regulation of TF on the surface of these cells can lead to a
11 systemic activation of the coagulation system that may progress to additional
12 complications such as disseminated intravascular coagulation (DIC). DIC is
13 characterized by the formation of microthrombi in microvasculature [23]. At the initial
14 stage clot formation occurs intra - and extravascularly due to thrombin activation
15 (hypercoagulopathy) and is followed by a consumption of coagulation factors
16 combined with a platelet dysfunction (hypocoagulability). This chain of events leaves
17 the patients in a paradoxical situation, where microvascular thrombus formation
18 causes a perturbation in the microcirculation, leading to multiple organ failure,
19 complicated by impairment of fibrinolysis. On the other hand patients experience a
20 high risk for severe bleeding due to depletion of coagulation factors and platelets
21 [24].

23 **Contact activation in severe infectious diseases**

24 With regard to the role of the contact system in severe infectious diseases it should
25 be noted that it was already in 1970 reported that patients with hypotensive sepsis
26 have significantly lower levels of contact factors in their blood than patients with
27 sepsis alone [25]. Since then, several studies have been published showing that
28 systemic contact activation has been found in patients with severe sepsis, septic
29 shock and sepsis combined with SIRS and that this is often combined with a massive
30 release of BK and a consumption of contact factors [26-28]. Notably, low levels of
31 plasma kallikrein, FXII and HK during sepsis correlate with a fatal outcome of the
32 disease [26, 29].

33 Until recently it was generally accepted that the contact system plays a secondary
34 role in hemostasis, since patients with deficiencies in FXII, plasma kallikrein, or HK
35 do not suffer from bleeding disorders. This point of view changed when the first data
36 on FXI and FXII deficient mice were published and it was found that contact
37 activation contributes to pathological thrombus formation in response to vessel injury

[30, 31]. Whether the contact system contributes to pathologic coagulation disorders in severe infectious diseases is controversial and discussed. For instance, Pixley and colleagues reported that contact activation occurs in patients with DIC [32]. Pronounced activation of the system was also seen in children with meningococcal septic shock [33, 34] and in patients with streptococcal toxic shock syndrome (STSS) [35]. On the other hand it has been found that patients with STSS but without a bleeding tendency, had a prolonged aPTT [35], implying that contact activation has occurred. The latter findings are in line with an experimental baboon model of lethal *E. coli* bacteremia, showing that systemic contact activation is not combined with DIC, but with fatal hypotension, probably caused by the release of BK [36, 37]. It is noteworthy to mention that animals experienced an initial hypotension that was reversed, when treated with a human antibody against FXII and extended the life of the baboons [36]. However, more studies are required to unravel the role of the contact system in the induction of coagulation disorders in severe infectious diseases.

Contact activation and inflammation

The release of BK from HK is responsible for evoking inflammatory reactions [38]. There are two types of kinin receptors in humans, termed B1 and B2 receptors. Mice lacking both receptors have normal blood pressure and cardiac morphology and they are unable to respond to stimulation with kinins [39]. Importantly, lipopolysaccharide (LPS) challenge in B1B2^{-/-} mice does not affect the blood pressure in these animals, while blood pressure was markedly decreased in wild-type animals [39]. Other studies have shown a protective effect of kinin antagonists in a lethal LPS model in rats [40]. With regards to the molecular mechanisms leading to the induction of these inflammatory reactions, Fischer *et al.* conducted experiments showing that BK-induced vasoconstriction in a rat LPS model can be prevented by the application of cyclooxygenase inhibitors and is dependent on the inducible nitric oxide synthase [41, 42]. These findings imply that the induction of second-generation mediators by kinins significantly contribute to the inflammatory reactions seen in the LPS challenged animals. Interestingly, many bacterial proteinases have evolved mechanisms to trigger the release of BK from HK, either by cleaving HK directly or by activating PK. One of the first reports was already published in 1984 by Matsumoto and colleagues who described a metallo protease from *Serratia marcescens* with plasma kallikrein-like properties [43]. Since then, bacterial proteinases from many other bacterial species have been described to activate the contact system in one way or another (for a review see [44]). It has been suggested that the vascular

1 permeability induced by the released kinins promotes an influx of plasma into the site
2 of infection that serves as nutrients and facilitates spreading of the microorganisms
3 within the infected host [44].
4

5 **Contact activation caused by microorganisms**

6 As early as 1983 it was shown by Kalter *et al.* that LPS of Gram-negative bacteria as
7 well as peptidoglycan and teichoic acid of Gram-positive bacteria have the ability to
8 induce activation of the contact system [45]. While the LPS binding-site in HK was
9 recently resolved [46], no information on the interaction sites between pepidoglycans
10 and teichoic acid with contact factors has been published to date. Subsequent
11 studies have shown that bacterial surface proteins, such as M protein of
12 *Streptococcus pyogenes* or thin aggregative fimbriae expressed by *Escherichia coli*
13 and *Salmonella*, are able to bind and assemble contact factors on their surfaces and
14 trigger the activation of the system [6, 47]. An activation of the contact system by
15 *Staphylococcus aureus* and *Rickettsia rickettsii* has also been described [7, 48]
16 although the bacterial proteins that promote the binding to the contact factors have
17 not yet been identified. In addition, and as mentioned above, many bacterial
18 proteinases have been described to cleave HK and release BK, and recently it has
19 been reported that fungal pathogens also (*Candida* species) interact with factors of
20 the contact system [49].
21

22 **Contact System Inhibition – a potential therapeutic intervention?**

23 One can wonder whether the contact system is an interesting target for drug
24 development, as it also has protective effects. For instance, it plays an important role
25 in innate immunity via the generation of HK-derived antibacterial peptides and kinin
26 induced recruitment of neutrophils [50-52]. However, these responses take place at
27 an early stage and are most likely restricted to the site of infection, while under
28 systemic conditions a massive activation of the contact system may lead to the
29 release of pathologic levels of kinins and a consumption of contact factors (for a
30 review see [26]). Notably, low levels of some contact factors are an indication of an
31 unfavorable outcome of the disease [26]. The prevention of a systemic activation
32 could therefore benefit seriously ill patients.

33 Kinins are potent inflammatory mediators, causing symptoms such as increased
34 vascular permeability, vascular leakage, hypotension and edema formation, which
35 are a hallmark of severe infectious diseases. Kinin receptors are therefore attractive
36 targets for drug development. Two receptors (B1R and B2R) have been described in
37 humans, of which both have completely different pharmacologic profiles (for a review

1 see [53]). B2R is constitutively expressed by most cell types and rapidly internalized
2 upon BK binding [53], while B1R is generally expressed at a low level in normal
3 tissue, but up-regulated upon stimulation with proinflammatory agents such as LPS
4 or endotoxins from *S. aureus* and *S. pyogenes* [54-56]. A number of kinin receptor
5 antagonists have been developed and successfully used in animal models [57].
6 However, so far only a B2R antagonist (Deltibant) has been used in clinical trials for
7 sepsis [58]. The drug was used in patients with SIRS and presumed sepsis in a
8 randomized, double-blind, placebo-controlled trial. Deltibant observed no significant
9 effect on risk-adjusted 28-day survival, but posthoc analysis of risk-adjusted 7-day
10 survival showed a non-significant trend toward improvement. Furthermore, the 28-
11 day risk-adjusted survival in the prospectively defined subset of patients with Gram-
12 negative infections showed a statistically significant improvement [58]. Considering
13 the important role of the B1R in infectious diseases [59], theoretically, a combination
14 of B1R and B2R antagonists could be an interesting alternative approach for a
15 clinical trial.

16 C1 inhibitor is a member of the family of serine proteinase inhibitors and a major
17 regulator of the complement and contact systems. It has been reported that levels of
18 proteolytically inactivated C1 inhibitor are increased in septic patients [60]. Notably,
19 treatment with C1 inhibitor during sepsis attenuated contact activation and had a
20 beneficial effect on hypotension and renal dysfunction [61-63]. The results from
21 clinical studies, therefore, indicate that therapeutic administration of C1 inhibitor may
22 be safe, even though major bleedings have been observed in patients as compared
23 to the control groups [62]. It should be noted that C1 inhibitor inhibits serine
24 proteases irreversibly and may also block other proteases from the coagulation
25 cascade, if applied in therapeutic doses.

26 A completely different mode of contact system inhibition was recently reported in a
27 mouse model of invasive streptococcal infections. In this study a synthetic peptide
28 derived from domain 5 of HK, resembling the binding site to eukaryotic and bacterial
29 surfaces (see above), was shown to prevent activation of the contact system on
30 these surfaces [64]. Treatment with the peptide protected mice with invasive
31 *Streptococcus pyogenes* infection from lung damage and, in combination with
32 clindamycin, the peptide also significantly improved the overall survival. However, the
33 peptide has not been used in clinical trials yet.

35 **Concluding remarks**

36 Therapies in sepsis, severe sepsis, and septic shock, which are entirely based on
37 antibiotics, are combined with a high risk to fail, and thus, there is an urgent need for

1 novel antimicrobial strategies. Concepts focusing on the prevention of patho-
2 physiological mechanisms in severe infectious diseases, such as the systemic
3 activation of important host effector systems, are therefore promising and may have
4 a considerable impact. For instance, treatment with activated protein C (APC) has
5 been found to reduce the mortality in severe sepsis patients [65]. However, APC
6 administration is combined with severe side effects (bleeding) and, thus, its
7 application is restricted to patients at high risk of death.

8 Patients with deficiencies in FXII, plasma kallikrein, or HK do not experience severe
9 bleeding disorders. The inhibition of the contact system at the initial stage of an
10 infection is therefore an interesting therapeutic approach to prevent hyper-
11 inflammatory reactions. This concept is in line with findings that the treatment of
12 sepsis patients with C1 inhibitor results in a beneficial clinical outcome. However, the
13 study also showed that patients still suffer from severe bleedings, probably because
14 C1 inhibitor also targets other coagulation factors apart from plasma kallikrein. It is
15 therefore tempting to speculate that more specific contact inhibitors with a safer
16 pharmacologic profile are promising candidates for the development of novel
17 antimicrobial therapies.

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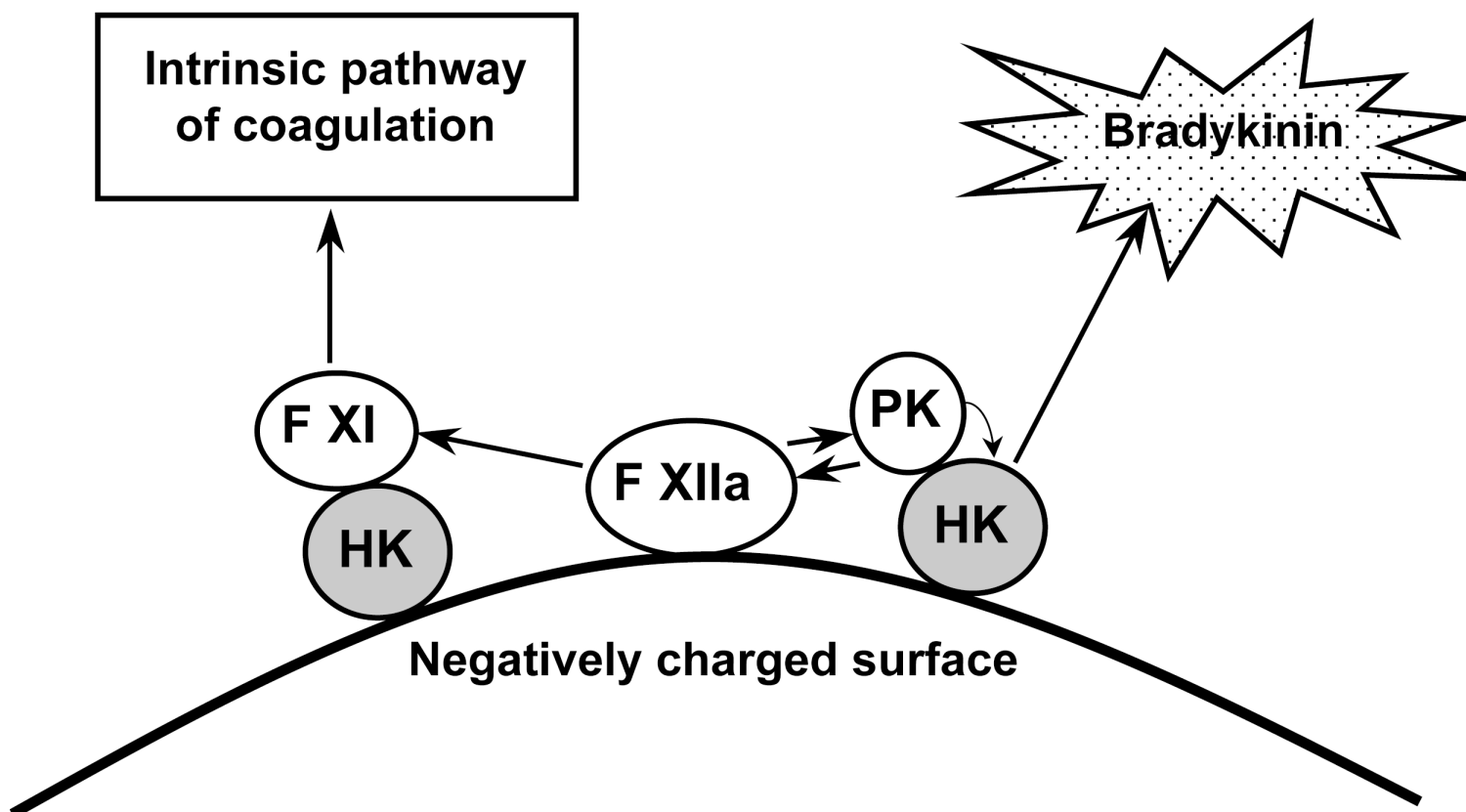
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1 Figure Legend:

2

3 Fig. 1: **The contact system.** Assembly of contact system factors on a negatively
4 charged surface activates FXII. FXII activates FXI that triggers the intrinsic
5 pathway of coagulation and plasma kallikrein. Plasma kallikrein cleaves HK,
6 followed by the release of the proinflammatory peptide BK.