The Plasma Contact System 2.0

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ABSTRACT

The contact system is a protease cascade that is initiated by factor XII activation on cardiovascular cells. The system starts procoagulant and proinflammatory reactions, via the intrinsic pathway of coagulation and the kallikrein-kinin system, respectively. The biochemistry of the contact system in vitro is well understood. However, activators of the system in vivo and their contributions to disease states have remained enigmatic. Recent experimental and clinical data have identified misfolded proteins, collagens, and polyphosphates as the long-sought activators of the contact system in vivo. Here we present an overview about contact system activators and their contributions to health and pathology.

KEYWORDS: Factor XII, polyphosphates, misfolded proteins, collagen, kallikrein-kinin system

THE COMPONENTS OF THE CONTACT SYSTEM

The contact system consists of four plasma proteins that assemble when blood comes into contact with negatively charged surfaces: factor XII (FXII, Hageman factor), factor XI (FXI), plasma prekallikrein (PK), and the nonenzymatic cofactor high molecular weight kininogen (HK). Factor XII and HK directly bind to polyanions, whereas PK and FXI are surface-bound via complex formation with HK.[1] Surface binding induces a conformational change in FXII that leads to limited proteolytic activity of the contact factor. Consecutively, activated FXII (α-FXIIa) cleaves FXI and PK generating activated FXI (FXIa) and plasma kallikrein. In an amplification reaction, formed kallikrein efficiently activates further FXII molecules.[2] A second cleavage of α-FXIIa by kallikrein generates the β-FXIIa form that consists of the active protease domain. β-FXIIa has lost its ability for surface binding and efficient FXI cleavage.[3] Kallikrein cleaves its cofactor HK to yield the peptide hormone bradykinin (BK).[4] When FXII becomes activated in vitro, there is concurrent activation of plasminogen by FXIIa and kallikrein[5] and activation of the classical pathway of the complement system involving C3 and C5.[6] Serine protease inhibitors regulate activity of the contact system. C1 esterase inhibitor (C1INH) and antithrombin (AT) are the endogenous inhibitors of FXIIa, FXIa, and kallikrein, respectively.

CASCADES TRIGGERED BY ACTIVATED FACTOR XII

Blood Coagulation: Activation of the Intrinsic Pathway

FXIIa triggers fibrin formation via its substrate FXI in the intrinsic pathway of coagulation.[7] Factor XII activation by kaolin (a silicate) is the molecular basis of a clinically used diagnostic clotting test, the activated partial thromboplastin time (aPTT). The aPTT assay tests the integrity of the intrinsic pathway and is commonly used to monitor heparin treatment. Moreover, it

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Forgotten Factors in Thrombosis and Hemostasis; Guest Editors, Marcel Levi, M.D., Ph.D., and Joost C.M. Meijers, Ph.D.

Semin Thromb Hemost 2011;37:375–381.
DOI: http://dx.doi.org/10.1055/s-0031-1276586.
ISSN 0094-6176.

is sensitive for the presence of lupus anticoagulant antibodies in plasma. Besides activation by FXIIa, FXI can also be activated by thrombin, providing a feedback activation mechanism that amplifies thrombin generation in response to tissue factor (TF) or FXIIa in vitro. This mechanism was originally identified in studies using purified coagulation factors[8] and was later refuted to proceed in plasma.[9] However, several recent studies provided evidence in favor of the existence of the originally proposed activation of FXI by thrombin.[10,11]

Kinin Formation: The Kallikrein-Kinin System

Bradykinin is the ligand of the kinin B2 receptor, a G-protein coupled receptor present on endothelial cells. BK induces vasodilation by stimulating cellular production of nitric oxide and induces symptoms of inflammation such as swelling, redness, and pain. In plasma, BK is converted to des-Arg^9-BK, which binds the kinin B1 receptor. This receptor is expressed in inflamed tissues and contributes to renal fibrosis, alterations in blood–brain barrier permeability, and regulation of adaptive immunity.[12,13] Bradykinin has a very short half-life in vivo (a matter of seconds) and is degraded by kininases, including angiotensin-converting enzyme (ACE).[14] The prolonged half-life of the vasodilator BK contributes to the blood pressure–lowering effects of ACE inhibitor treatment. Conversely, dry cough and respiratory reactions, known adverse effects of ACE inhibitors, are attributed to elevated BK levels.

Proteolysis and Innate Immunity: Plasminogen and Complement Activation

FXIIa and kallikrein activate plasminogen in plasma,[5] resulting in plasmin formation. Plasmin is the principal enzyme that degrades fibrin meshworks. Plasminogen activation by FXIIa may be due to the high homology of FXII and tissue plasminogen activator (tPA), a fibrinolysis initiator.[15] The catalytic sites of the proteases are also similar; both tPA and FXIIa are inhibited by corn trypsin inhibitor (CTI).[16] On cell surfaces, plasminogen activation is triggered by BK-stimulated release of tPA from endothelial cells.[17] Conversely, in patients, endothelial cell activation is associated with elevated FXII-dependent fibrinolytic activity.[18] Independent of its effects on fibrinolysis, FXII-driven plasmin formation contributes to tissue remodeling, regulation of cell differentiation, and wound healing.[19–21] The contact system has the capacity to activate the classical pathway of the complement system,[6] and simultaneous activation of the contact and complement system often occurs in pathological conditions. The inhibition of multiple contact system components by C1INH is also indicative of the relationship between both systems.

CLINICAL PRESENTATION OF CONTACT SYSTEM FACTOR DEFICIENCIES

Factor XII Deficiency

Factor XII was originally discovered by chance after the seminal observation that plasma of the index patient for FXII deficiency, John Hageman, failed to clot in a glass vial.[22] In contrast to defective in vitro clotting tests, there is no apparent bleeding tendency in people who are partially or completely deficient in FXII. Today it is generally accepted that deficiency in FXII has no importance for hemostasis (fibrin formation at a wound site) and is not associated with any abnormal spontaneous or injury-related hemorrhage. Based on the death of Hageman by a massive pulmonary embolism and other anecdotal case reports, it was suggested that FXII deficiency is associated with increased risk for thrombotic disease.[23] However, large epidemiological studies failed to find a correlation between low FXII levels and an increased incidence of deep vein thrombosis,[24] and FXII was lower in myocardial infarction patients versus controls. Recent data showed that FXII-driven fibrin formation has a critical role for mechanical clot stability.[25] Deficiency in this pathway may result in reduced clot firmness and might increase the risk for embolic complications; more studies are necessary, however, to support this hypothesis.

Plasma Prekallikrein and High Molecular Weight Kininogen Deficiency

Deficiencies in PK or HK are rare in humans. Severe HK deficiency is usually associated with low FXI levels, presumably due to decreased half-life of the protease in the absence of the complex partner. Although the aPTT is prolonged in HK- or PK-deficient individuals, they have no obvious bleeding problem. Similarly, PK deficiency does not obviously compromise fibrinolysis, leukocyte functions, or inflammatory responses,[26] suggesting that scenarios for critical HK/PK activation have not been yet identified or that alternative systems may exist that compensate for deficiency in the contact factors.

C1 Esterase Inhibitor Deficiency

Congenital deficiency in a functional C1INH leads to hereditary angioedema (HAE), a severe swelling disease with painful and sometimes life-threatening obstructive histamine-independent episodes of edema.[27] The swelling attacks are due to excessive BK generation driven by FXII-dependent kallikrein activity. So far, the trigger for FXII activation in HAE is unknown, and increased estrogen levels, trauma, infections, or stress have been inconsistently linked to the onset of the swelling episode. An HAE variant with

Table 1 Overview of Factor XII Activators and Their Effects on FXII-Dependent Coagulation or Inflammation

	In Vitro Effect		In Vivo Effect	
Compound	Intrinsic Coagulation Pathway	Kallikrein-Kinin System	Procoagulant	Proinflammatory
Nonphysiological materials				
Glass	+	+	+	+
Kaolin	+	+	+	+
Ellagic acid	+	+	−	+
Dextran sulfate (high molecular weight)	+	+	−	+
Ellagic acid	+	+	−	+
Oversulfated chondroitin sulfate	−	+	−	+
Poly I:C	+	+	+	?
Biomaterials				
Dialysis membranes				
Cuprophane/Polyacrylonite/AN69) for example	+	+	+	+
Vascular grafts				
(Dacron/PTFE/ PDMS)	+	+	?	?
Metal (steel/titanium/aluminum)				
Therapeutical compounds	+	+	?	?
Aptamers	+	+	?	?
Iron oxide nanoparticles	?	+	?	+
Endogenous substances				
Glycosaminoglycans	−	+	?	?
Nucleic acids (RNA, DNA)	+	+	?*	?
Sulfatide	+	+	+	+
Urate crystals	+	+	?	+
Misfolded protein aggregates	−	+	−	+
Polyphosphates	+	+	+	+
Amyloid β peptide	−	+	−	+

*Administration of RNAse that degrades RNA provides thromboprotection in mice.

normal C1INH function was described that is associated with a single point mutation in FXII that translates into an amino acid substitution (Thr328Lys).[28] During acute HAE attacks, there is also activation of the fibrinolytic system and complement systems.[29] Intriguingly, although the FXII-driven contact system is highly active in HAE episodes, patients do not display an increased thrombotic tendency. This suggests that selective and specific activation modes for FXII exists that trigger either the kallikrein-kinin system and/or the intrinsic pathway of coagulation. Administration of plasma-derived or recombinant C1INH has become the preferred treatment in episodes of HAE. Alternative therapeutic options are the direct kallikrein inhibitor Ecallantide (DX-88)[30] or the peptidergic kinin B2 receptor antagonist Icatibant/HOE 140.[31]

ACTIVATORS OF THE CONTACT SYSTEM IN VITRO

An overview of activators of the contact system in vitro is given in Table 1.

Silica-Based Materials

Glass was one of the first substances described to activate FXII. The white clay minerals kaolin and celite, two other silica-rich compounds, are the most commonly used FXII activators for coagulation diagnostics. Kaolin is also used to terminate blood loss after serious injury.[32] Although the idea of employing the contact system to seal injuries is interesting, exposing flowing blood to kaolin triggers thromboembolic events[33] and may not be applicable for all sorts of injury.[34]

Negatively Charged Polymers: Sulfated Polysaccharides

FXII is activated when it binds to polymeric negatively charged polysaccharides. One of the best characterized FXII contact activators is dextran sulfate (DXS), a polysulfated polysaccharide of glucose moieties. DXS-mediated FXII activation is critically dependent on the chain length and degree of sulfation of the polyanion.[35] High molecular weight DXS (500 kDa) is a potent stimulator of FXII, whereas shorter DXS polymers fail to activate FXII. When injected in large animals, long-chain DXS

induces bradykinin-mediated hypotension[36] but does not trigger intravascular coagulation. Polysaccharide-stimulated BK generation may have fatal effects. During 2007 and 2008, 149 patients died from anaphylactic hypotension associated with intravenous heparin treatment. Oversulfated chondroitin sulfate (OSCS), a not naturally occurring polysaccharide, was identified and characterized[37] as the culprit heparin contaminant. OSCS activates the kallikrein-kinin and complement systems as potently as DXS. Dextran sulfate may have physiological analogues; mast cell–derived chondroitin sulfates have been proposed as activators of the kallikrein-kinin system in vitro.[38] However, the physiological relevance of this mechanism has not been elaborated so far.

Polyphenolic Compounds: Ellagic Acid

A classical activator of FXII is ellagic acid (2,3,7, 8-Tetrahydroxy-chromeno[5,4,3-cde]chromene-5,10-dione; EA). In vitro, EA triggers FXII-driven coagulation,[39] and the substance is commonly used as a starter for the aPTT assay. Infusion of EA into humans leads to a "hypercoagulable state".[40] However, it remains unclear whether this is due to direct FXII activation, EA effects on platelet aggregation, or a combination of both. Besides inducing clot formation, EA also activates the fibrinolytic system,[41] and when administered in vivo it reduces blood pressure presumably involving BK activity.[42]

NEW ACTIVATORS OF FACTOR XII

Recent studies in FXII-, FXI-, and kininogen-deficient mice have shown that the contact system has a critical role for pathological thrombus formation in vivo. Severe deficiency in any of the contact factors abolished formation of vessel-occlusive clot formation induced by various types of injury in arterial and venous vascular beds.[43–45] Consistent with contact factor-deficient patients, deficiency states were not associated with increased bleeding in mice. The essential role of the contact system for thrombosis albeit being dispensable for hemostasis indicates that FXII-driven fibrin production proceeds within the growing thrombus but is of minor importance at a site of vascular injury.[46,47] In contrast, FXII is believed to stimulate bradykinin production on endothelial cell surfaces at the vessel wall.[4,14]

Misfolded Protein Aggregates: Protein Activators of the Kallikrein-Kinin System

Activation of the contact system contributes to a number of pathologies, one of which is Alzheimer's disease (AD).[48] Bradykinin is produced in the cerebrospinal fluid of AD patients,[49] probably due to a direct FXII-dependent kallikrein activation initiated by aggregates of amyloid β peptide.[50] In addition to aggregated amyloid β peptide, FXII is activated by a variety of other misfolded protein aggregates. In patients suffering from systemic amyloidosis, a disease in which aggregates of immunoglobulin light chains circulate and deposit, FXII-driven activation of the kallikrein-kinin system proceeds[51] with concurrent plasmin activation.[52] Misfolded protein aggregates specifically trigger the kallikrein-kinin system but do not activate the intrinsic pathway of coagulation in plasma or in a reconstituted system.[51] One possible explanation for the selective activation of PK could be that local concentrations of PK molecules exceed those of FXI.[53] However, both zymogens are surface bound via HK and share a conserved HK-binding site.[1,54,55] Moreover, negatively charged surfaces like kaolin do support FXII-dependent FXI activation under the same circumstances. Factor XII differs in binding to negatively charged surfaces and misfolded protein aggregates with possible implications for substrate preferences. Surface binding is mediated through the fibronectin type 2, second EGF, and kringle domains,[56,57] whereas interaction to aggregates is mediated by the fibronectin type 1 domain.[58] Differences in FXII binding may also modulate the conversion of α-FXIIa to β-FXIIa by kallikrein and shift FXII activity toward kinin formation. Oversulfated chondroitin sulfates augment activity of protease inhibitor AT, which preferentially blocks FXIIa-driven procoagulant activity.[37] Similar mechanisms possibly operate on aggregated proteins. The structural basis of the interactions of misfolded proteins with FXII and its importance for health and disease remain to be elucidated.

Collagen

It was reported >40 years ago that FXII binds to insoluble collagen, enhancing coagulation.[59] The interaction depends on a repetitious presentation of negative charges in the native collagen fibril.[59] However, later reports argued against a direct activation of FXII by collagen. Recent studies have reevaluated the importance of collagen for FXII activation.[60] Factor XII was shown to bind to collagen fibrills of various origins. When added to plasma, (equine) type I collagen promoted thrombin formation and plasma clotting in an FXII-dependent manner. Factor XII activity is critical for collagen-stimulated thrombus formation in flow chambers.[61] Additionally, collagens may stimulate the contact system indirectly.[25]

When blood contacts collagen under flow, the FXIIa inhibitor CTI blocks platelet activation.[60] This suggests that thrombin, which is formed via the collagen-stimulated intrinsic pathway, propagates platelet activation. Recent studies argue for direct effects of FXIIa on the protease-activated receptor (PAR3),[62] which may contribute to contact system–driven platelet activation. PAR3 receptors are only expressed on murine platelets, limiting the consequences of this mechanism

for thrombosis in humans. Taken together, these reports suggest that activation of FXII proceeds on or near procoagulant platelets.

Activated Platelets and Polyphosphates

Platelets support FXII activation, dependent on integrin αIIb-β3 signaling,[63] and enhance activation of the kallikrein-kinin system in plasma.[64] Moreover, platelets support the activation of FXII and FXI in the presence of thrombin and TF inhibition,[65] showing that platelets specifically trigger the intrinsic coagulation pathway. Recent studies identified the platelet-derived FXII-activator polyphosphate (polyP), an inorganic polymer of 60 to 100 phosphate residues. Polyphosphate was originally identified in nonmammalian cells but was later shown to be enriched in platelet-dense granules.[66] Platelet polyP activates FXII in reconstituted systems and in plasma[67] via direct binding.[25] PolyP-stimulated FXIIa initiates thrombin and BK formation in an FXI- and PK-dependent manner, respectively. In mice, platelet-secreted endogenous polyP induces pathological thrombus formation (pulmonary embolism) and BK-driven edema. Targeting polyP with phosphatases, which enzymatically degrade polyP, almost completely abolished procoagulant platelet activity and largely protected animals from activated platelet–driven thrombosis in vivo. Together, the data highlight the importance of polyP as an endogenous activator of the FXIIa-driven contact system in vivo. Synthetic polyP restored defective clot formation in platelet-rich plasma from Hermansky-Pudlak patients, who suffer from hereditary polyP deficiency,[25] suggesting that polyP may be used as a hemostatic agent.[68]

OUTLOOK

For decades, FXII-triggered coagulation activity was believed to be a test tube phenomenon with no importance for fibrin formation in vivo. Recent human and animal studies convincingly demonstrated that the FXIIa-driven intrinsic pathway of coagulation is essential for thrombosis but of minor (if any) importance for hemostasis. Factor XII activation occurs on procoagulant platelets driven by polyP, supporting the critical role of FXII for thrombosis.

Given that activated platelets release polyP at the wound side, why is FXIIa activity dispensable for ceasing blood loss at a side of injury? Fibrin formation triggered by the TF "extrinsic" pathway may be sufficient to stabilize the platelet aggregate and to seal sites of injury. In contrast, additional coagulation activity provided by polyP-triggered FXIIa-mediated intrinsic pathway is necessary for generating fibrin that stabilizes thrombi under flow.[7] Elucidating the relative importance of TF- and FXIIa-driven fibrin formation for hemostasis and thrombosis is one of the major challenges for the future.

In conclusion, recent biochemical, animal, and patient studies have initiated a revival of the contact system and provided detailed insights into mechanisms that initiate the system in disease states. However, the physiological roles of the system remain to be identified.

ACKNOWLEDGMENTS

This article was supported in part by the EU-funded ERARE, Hjärt-Lungfonden (20090642), and Vetenskapsrådet (K2010-64X-21462-013) grants to Thomas Renné and a grant of the Netherlands Organization for Scientific Research (NWO) to Coen Maas (NWO-Rubicon: 825-10-012).

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